Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2004-08

Methoxyfenozide

The active ingredient (a.i.) methoxyfenozide and its associated end-use product (EP) Intrepid 240F Insecticide, which contains 240 g/L of the active ingredient and is used to control certain lepidopteran larvae on apples, have been granted temporary registration under Section 17 of the Pest Control Products (PCP) Regulations.

This Regulatory Note provides a summary of data reviewed and the rationale for the regulatory decisions concerning these products.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration for the technical grade active ingredient, methoxyfenozide, and the associated end-use product, Intrepid 240F Insecticide for the control of certain lepidopteran larvae on apples.

Methods for analysing methoxyfenozide in environmental media are available to research agencies upon request to the PMRA.

Dow AgroSciences will be carrying out additional environmental fate and ecotoxicity studies as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed regulatory decision document and request comments from interested parties before proceeding with a final regulatory decision.

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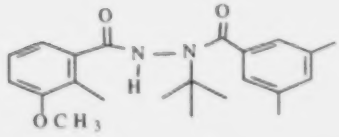
1.0 The active substance, its properties and uses

1.1 Identity *(OECD 2.1.1)*

TGAI identification

Active substance	Methoxyfenozide
Function	Insecticide
Chemical name	
IUPAC	N-tert-butyl-N'-(3-methoxy-o-toluoyl)-3,5-xylohydrazide
CAS	Benzoic acid, 3-methoxy-2-methyl-, 2-(3,5-dimethylbenzoyl)-2-(1,1-dimethylethyl) hydrazide
CAS number	161050-58-4
Molecular formula	$C_{22}H_{28}N_2O_3$
Molecular weight	368.47
Structural formula	
Nominal purity of active	98.2% (limits: 95.9–100%)
Identity of relevant impurities of toxicological, environmental or other significance	The technical grade methoxyfenozide does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances. The product is contaminated with 1,1-dimethylhydrazine at a maximum of < 1 ppm.

1.2 Physical and chemical properties *(OECD 2.1.2)*

Technical product: Methoxyfenozide

Property	Result	Comment
Colour and physical state	White powder	
Odour	Faint odour	
Melting point or range	206.1–208°C	
Boiling point or range	Not applicable	

Property	Result	Comment
Specific gravity	0.740 ± 0.0081	
Vapour pressure	< 1×10^{-7} torr (< 1.33×10^{-5} Pa) at 25, 35 and 45°C	Non-volatile
Henry's Law constant at 20°C	1.935×10^{-7} atm·m^3/mol	Non-volatile from moist soils or water
UV-visible spectrum	No absorption expected at $\lambda > 300$ nm	Low potential for phototransformation
Solubility in water at 20°C	3.3 mg/L	Low solubility
Solubility in organic solvents at 25°C	Solvent / Solubility (g/kg): n-heptane 1.87; xylene 3.38; CH_2Cl_2 36.72; methanol 192.92; 2-propanol 50.22; acetone 126.88; butyl acetate 8.76	In general, solubility appears to increase with increasing organic solvent polarity
n-octanol–water partition coefficient (K_{ow})	log K_{ow} = 3.72 ± 0.04 at 24.7 ± 1.4°C	Potential for bioaccumulation
Dissociation constant (pK_a)	None	
Stability (temperature, metal)	Stable to hydrolysis at pH 5, 7 and 9 and in water under irradiation.	

End-use product: Intrepid 240F Insecticide

Property	Result
Colour	White
Odour	Weak characteristic odour
Physical state	Liquid
Formulation type	Suspension
Guarantee	240 g/L (limits: 233–247 g/L)

Property	Result
Formulants	The product does not contain any USEPA List 1 formulants or formulants known to be Toxic Substances Management Policy (TSMP) Track 1 substances.
Container material and description	10 L HDPE jug (recyclable) 110 L HDPE "mini-bulk" or "tote" (returnable) "Bulk" truck or railway metal container (returnable)
Specific gravity	1.06
pH	6.6 (undiluted)
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agents.
Storage stability	Data showed that the product is stable for two years at ambient temperature in HDPE bottles.
Explodability	The product is not explosive.

1.3 Details of uses

Dow AgroSciences has applied for registration of Intrepid 240 F Insecticide, a commercial end-use product that contains 240 g/L of the new active ingredient methoxyfenozide. Intrepid 240 F is to be used on apples for control of codling moth, Oriental fruit moth, the overwintering generation of oblique-banded and three-lined leafrollers, and the first generation of western tentiform and spotted tentiform leafminers. This product will also suppress the winter moth and the summer generation of oblique-banded and three-lined leafrollers on apples. Application rates are as follows:

- 1.0 L product/ha for codling moth and Oriental fruit moth,
- 0.75 L product/ha for leafrollers and wintermoth, and
- 0.5 L product/ha for leafminers.

The maximum amount of product that can be applied is 2 L product/ha/year (480 g a.i./ha/year) and application is by ground only.

The active ingredient of Intrepid 240F Insecticide, methoxyfenozide, belongs to the diacylhydrazine class of insecticides, which are second generation ecdysone agonists. The mode of action is primarily by ingestion. Because Intrepid 240 F Insecticide must be ingested by Lepidopteran larvae to have an effect, timing of application is dependent on the feeding behaviour of the target pest. Correct application timing and thorough uniform coverage of all foliage and fruit is essential for consistent performance.

2.0 Methods of analysis

2.1 Analytical methods for analysis of the active substance as manufactured

The active ingredient and major impurities in the technical product were determined by reversed phase liquid chromatography with UV detection (RPLC-UV). The method was found to give acceptable range of mean recoveries [96–128% depending on the analytes], relative standard deviations [0.7–8.7%] and limits of quantitation [0.01–0.04%]. Representative chromatograms of standards and samples show no interferences and suggest that the method is sufficiently specific for the determination.

2.2 Analytical methods for formulation analysis

The active ingredient in Intrepid 240F was determined by liquid chromatography with UV detection (LC-UV). The method was found to give good mean recovery [99.5%] and acceptable relative standard deviation [1.12%, n = 12]. Representative chromatograms of the methoxyfenozide technical product and formulation blank show no interferences around the retention vicinity of the active ingredient and suggest that the method is sufficiently specific for use as the enforcement analytical method.

2.3 Methods for residue analysis

2.3.1 Multi-residue methods for residue analysis

A multi-residue method for testing methoxyfenozide was conducted according to the Pesticide Analytical Manual Volume 1 (PAM Vol. 1; revised January 1994). The fatty matrix was cottonseed oil and the non-fatty matrix was apple. As described below, methoxyfenozide was not recovered efficiently using the protocols in the PAM Vol. 1 Multi-residue Methods. Therefore, the existing multi-residue methods were not suitable for the determination of methoxyfenozide residues.

Protocol A: Methoxyfenozide was not tested through Protocol A since it does not possess an N-methylcarbamate structure.

Protocol B: Methoxyfenozide was not tested through Protocol B since it does not contain a carboxylic acid or a phenolic moiety.

Protocol C: This protocol examines gas chromatographic detectability of methoxyfenozide in relation to chlorpyrifos. Methoxyfenozide was dissolved in acetone and tested using various gas chromatography columns (DB-17, DB-1 and DB-225) with electron capture (EC) detection or nitrogen phosphorus (NP) detection. There were unacceptable recoveries with all methods except with the DB-1 column using EC detection when column temperature was increased to 255°C (level II evaluation). Based on these responses methoxyfenozide was not evaluated under Protocol D.

Protocol D: Methoxyfenozide was not tested under Protocol D because it was only detected using EC dctection under Protocol C.

Protocol E: Analysis of methoxyfenozide using DB-1 with EC detection that was found to be acceptable during Protocol D evaluation, showed no recovery for this compound from Florisil columns using either the mixed ether or methylene chloride elution system. Therefore, no additional work was performed on methoxyfenozide under Protocol E.

Protocol F: An evaluation through Protocol F was not conducted due to unacceptable recovery through Protocol E.

2.3.2 Methods for residue analysis of plants and plant products

In plants, the residue of concern (ROC) for enforcement and risk assessment purposes was defined as methoxyfenozide. Four analytical methods for the analysis of methoxyfenozide in plants were proposed.

Enforcement Method TR 34-98-87 is an HPLC-UV method for analysis of methoxyfenozide in pome fruit. This method was used for data-gathering and enforcement purposes. Briefly, samples were extracted in methanol:aqueous 0.1 N HCl followed by liquid-liquid partitioning in hexane and methylene chloride. After further purification on silica gel and/or Florisil and/or C18 columns, depending on the matrix, samples were analyzed by HPLC-UV (240 nm). Based on unacceptable recoveries and poor repeatability/precision measures for pear at the 0.01 ppm spiking level and also based on additional chromatographic evidence from the apple residue trial studies, it was recommended that the limit of quantitation (LOQ) for pome fruit be adjusted to 0.025 ppm. Apple, pear, processed apple juice and wet apple pomace samples spiked from 0.025–11 mg/kg showed fair recoveries (57.1–131% in all matrices and over all spiking levels). The independent laboratory validation (ILV) of Method TR 34-98-87 in apple fruit indicated good reproducibility. Method TR 34-98-87 is, therefore, considered acceptable as a data-gathering and enforcement method for pome fruit.

Preliminary Method TR 34-98-186 determines residues of methoxyfenozide in grapes, peppers, tomatoes as well as leafy and cole crops by HPLC-UV (or by HPLC-MS for celery). Since the method was not intended for enforcement purposes, an ILV was not required. Briefly, acidic methanol was added to the samples, which were then partitioned with hexane and methylene chloride. To further purify the extract, basic alumina column chromatography was then carried out followed by Envir-carbon Solid Phase Extraction (SPE), except in the case of celery. Quantitation of the extracted residues was then achieved by HPLC-UV. For celery samples, C-18 SPE was used rather than the carbon SPE and subsequent quantitation of the residues was by HPLC-MS. The LOQ for all matrices was 0.02 ppm. The limit of detection (LOD) was not explicitly stated in this report, but was explicitly stated to be 0.006 ppm in other reports (i.e., freezer storage

stability studies) where the method was used for residue analysis. Quantitation of residues from spiked samples was achieved using a calibration curve of external RH-2485 standards.

Method validation of TR 34-98-186 was carried out on a total of 23 different matrices to represent raw agricultural commodities (RACs) and processed fractions from grapes, peppers, tomatoes as well as leafy and cole crops. A complete list of matrices tested includes the following:

- red and white grapes;
- red grape and white grape juice;
- red wine;
- green peppers, red bell peppers, jalapeno peppers and chili peppers;
- tomatoes, cherry tomatoes and plum tomatoes;
- tomato juice, tomato puree and tomato paste;
- celery;
- red and green cabbage;
- leaf and head lettuce;
- spinach and mustard greens; and
- broccoli.

Samples (n=101) spiked with methoxyfenozide at a variety of levels ranging from 0.02–10 ppm, all had recoveries within the acceptable range (70–120%). Method TR 34-98-186 was considered acceptable as a data-gathering method for grapes, peppers, tomato as well as leafy and cole crops.

Residue Analytical Method TR 34-99-26 determines methoxyfenozide residues in various stone fruit matrices including cherries, peaches, plums, prunes and prune juice by HPLC-UV. Method TR 34-00-109 was also submitted as the enforcement method for the same matrices and was described as an identical method to TR 34-99-26. The difference between the two reports revolves around the inclusion of additional validation data. Consequently, only Method TR 34-99-26 is summarized and its review was also considered adequate to support the enforcement method. Briefly, the samples were extracted with acidic methanol followed by hexane and methylene chloride partitioning. The extract was then purified by basic alumina column chromatography and carbon SPE. Finally, quantitation was carried out by HPLC-UV. Quantitation of residues from spiked samples was achieved using a calibration curve of external RH-2485 standards. The LOQ was 0.02 ppm and the LOD was 0.006 ppm.

Method validation of TR 34-99-26 was carried out using three representative RAC matrices (cherries, peaches and plums) and two processed matrices (prunes and prune juice). Recoveries from samples spiked with methoxyfenozide at levels ranging from 0.02–1.0 ppm (0.5 ppm for cherry) were all within the acceptable range (70–120%). An ILV carried out on Method TR 34-99-74 (a method identical to TR 34-99-26, with an

added specification for celery) confirmed the reproducibility of the method. Method TR 34-99-26 is, therefore, considered acceptable as a data-gathering and enforcement method for stone fruit.

Preliminary Residue Analytical Method TR 34-95-133 is a data-gathering method to measure residues of methoxyfenozide in cotton by HPLC-UV. The method was used in an associated freezer storage stability study on cotton. Briefly, the samples were extracted with acidic methanol followed by refluxing at 65–70°C under reduced pressure. The samples were then filtered; subsequently, hexane and methylene chloride partitioning was carried out to remove the polar compounds. Subsequently, basic alumina column chromatography and Envir-carbon column chromatography were used to further purify the extract. Quantitation of the purified extract was by HPLC-UV and by using a calibration curve generated with external RH-2485 standards. The LOQ was 0.025 ppm and the LOD was 0.0075 ppm. Method validation was conducted using cotton seed samples. Recoveries of RH-2485 from 37 cotton seed samples spiked with methoxyfenozide at multiple levels (0.01–0.25 ppm) ranged from 58.9–134%. Although six of the samples had recoveries outside of the acceptable range (70–120%) the mean recoveries from each spiking level were acceptable (83.3–111.1%).
Method TR 34-95-133 is, therefore, considered acceptable for data-gathering purposes for cotton.

2.3.3 Methods for residue analysis of food of animal origin

For animal matrices, the ROC for risk assessment and enforcement purposes in milk and tissues of ruminants (except liver and kidney) was defined as the parent compound, methoxyfenozide. In the liver and kidneys of ruminants, the ROC was defined as methoxyfenozide plus the metabolite RH-141518.

Preliminary Residue Analytical Method TR 34-98-106 was proposed for data-gathering purposes for residues of methoxyfenozide and metabolite RH-141518 in bovine commodities (milk, cream, fat, muscle, liver, kidney). Briefly, milk was extracted with dichloromethane (DCM) using matrix solid phase dispersion (MSPD), then re-dissolved in ethyl acetate:hexane and further purified by Alumina Column Chromatography and carbon SPE. Muscle was extracted with DCM using MSPD, then re-dissolved in ethyl acetate:hexane and further purified by alumina column chromatography and carbon SPE. Fat was extracted with methanol:aqueous HCl and then by liquid-liquid partitioning into DCM. Further purification was by alumina column chromatography and carbon SPE. Milk, cream, fat, and muscle samples were analyzed by HPLC-UV (240 nm). Liver and kidney samples were first extracted with methanol followed by partitioning with hexane. Subsequently, two subsamples for each tissue were subjected to different partitioning and purification techniques: one underwent purification on C-18 and carbon SPE columns and the other underwent partitioning into DCM and purification by alumina column chromatography. Liver and kidney samples were analyzed by HPLC-MS. The reported LOQs were 0.01 ppm for methoxyfenozide in all matrices, and 0.02 ppm for the metabolite RH-141518 in kidney and liver. The method was not validated for cream.

Radiolabelled milk and tissue samples from the goat metabolism study were analyzed using method TR 34-98-106. For methoxyfenozide, there was 67% average accountability of residues in milk and 85–94% average accountability of residues in fat, kidney and liver, thus indicating acceptable recovery. For RH-141518, there was 41% average accountability of residues in kidney and 104% average accountability of residues in liver. However, there was no radiolabelled standard for RH-141518 in this study, and results have not been accurate. Therefore, radiovalidation of the method for RH-141518 was incomplete.

Method validation was carried out in milk, fat and muscle. Recoveries of the parent from milk, fat, and muscle samples spiked with methoxyfenozide over the range of 0.01–1.0 ppm were all acceptable (67–118 ± 11.3% in milk; 70–104 ± 6.6% in fat; 63–118 ± 11.1% in muscle).

Preliminary validation data for liver and kidney were not reported because inconsistencies were noted in the RH-141518 results in the liver between the analytical method reports for the preliminary method for bovine liver and kidney (TR 34-98-67) and the data-gathering method developed for all bovine commodities (TR 34-98-106). The ILV of Method TR 34-98-106 in bovine liver, indicated good reproducibility. The PMRA has determined that this method was valid provided that minor revisions relating to liver and kidney matrices, as recommended by the USEPA, are incorporated. The USEPA has reported that the revised method will be forwarded for publication in the PAM, Volume II.

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

Toxicokinetic studies indicated that methoxyfenozide was rapidly and substantially absorbed by the oral route (60–70% of the administered dose). It was also rapidly excreted via the feces and to a lesser extent in urine (91–100% of the administered dose 48 hours following administration). Results suggested slight gender differences with regard to hepatic and/or renal handling/metabolism of methoxyfenozide.

The data suggest that methoxyfenozide does not bioaccumulate. The liver was the organ with the highest residue levels. Methoxyfenozide was extensively metabolized; the parent compound and 33 metabolites were found in the feces and urine. Eight metabolites, including the parent compound, were identified. These metabolites were present at greater than or equal to 5% of the administered dose and accounted for 74–90% of the administered dose. The majority of metabolites were recovered in feces.

Methoxyfenozide was of low acute oral (LD_{50} > 5000 mg/kg bw), dermal (LD_{50} > 5000 mg/kg bw) and inhalation (LC_{50} > 4.3 mg/L) toxicity; it was minimally irritating to the eyes, but was not a skin irritant or a skin sensitizer. The end-use formulation, Intrepid 240F Insecticide, was of low acute oral (LD_{50} > 5000 mg/kg bw)

and dermal (LD_{50} > 2000 mg/kg bw) toxicity and showed no signs of acute inhalation toxicity at a maximum attainable chamber concentration of 0.9 mg/L. The formulation was not an eye or skin irritant or a skin sensitizer. The demethylated metabolite of methoxyfenozide, RH-117236 (M-B), also was of low acute oral toxicity (LD_{50} > 5000 mg/kg bw).

Results from short- and long-term oral toxicology studies indicate that generally the toxicological effects of methoxyfenozide are observed only at relatively high doses (in many studies, effects were observed only at doses greater than or equal to the limit dose) and that toxicity increased with increased duration of dosing (rats, dogs). Alterations in hematological parameters (decreased red blood cell [RBC] counts, hemoglobin and hematocrit, increased methemoglobin, and increased platelets), increases in bilirubin levels, and effects on the liver (periportal hepatocellular hypertrophy, increased liver weight), thyroid (hypertrophy, altered colloid), and adrenals (increased weight) were the most significant effects reported. The dog displayed slightly greater sensitivity to the blood effects than the rat and mouse. A 4-week dog recovery study provided evidence that the affected hematological parameters were reversible. The no observed adverse effect levels (NOAELs) from the two-year rat study and the one-year dog study were comparable at 10.2 and 9.8 mg/kg bw/day, respectively. Short-term repeated dermal dosing in the rat failed to elicit toxicity at the limit dose for testing (1000 mg/kg bw/day).

Methoxyfenozide was not a developmental, reproductive or nervous system toxicant. Study results did not indicate that young animals were more sensitive to the effects of methoxyfenozide than adults.

Results of the chronic and genotoxicity (in vivo, in vitro) studies indicated that methoxyfenozide was not a carcinogen or a genotoxicant. A major metabolite, RH-117236 (M-B) was non-mutagenic in the Salmonella/Ames Assay.

Effects on endocrine organs (thyroid and adrenals), were observed at relatively high doses only.

3.2 Determination of acceptable daily intake

The acceptable daily intake (ADI) of 0.10 mg/kg bw/day was based on the combined NOAELs of the rat chronic/oncogenicity study and the one-year dog study. These studies are of the appropriate duration and provide the lowest NOAELs in the supporting toxicology database.

In the rat, a NOAEL of 10.2 mg/kg bw/day was based on liver enzyme changes and thyroid effects at 411 and 491 mg/kg bw/day (for males and females respectively). Marginal changes in RBC parameters and adaptive liver changes were observed at the NOAEL. In the dog study, the NOAEL of 9.8 mg/kg bw/day was set on the basis of hematological changes observed at 106 and 111 mg/kg bw/day (for males and females

respectively). The dog demonstrated a slightly greater sensitivity to the hematological findings when compared to the rat and mouse.

An uncertainty factor of 100 (10× for intraspecies variations and 10× for interspecies variations) was considered adequate. No additional uncertainty/safety factors were required as there was no evidence of increased sensitivity in fetuses and/or pups provided in the developmental and reproductive studies. Further, results of the neurotoxicity studies did not warrant the need to conduct a developmental neurotoxicity study and the database was thus considered complete.

3.3 Acute reference dose

There were no toxicological effects in any of the studies that could be attributed to the administration of a single dose of methoxyfenozide. Therefore, an acute reference dose (ARfD) was not determined.

3.4 Toxicological endpoint for assessment of occupational, residential and bystander risks

The risk assessment considered exposure scenarios to the professional applicator, re-entry worker and bystanders. During the mixing, loading and application of methoxyfenozide, exposure to the professional applicator is considered intermittent over a short-term duration (4–6 weeks). Exposure to the re-entry worker is considered to occur daily over an intermediate term (2–3 months). For bystanders, exposure is considered to be acute (1–2 days). The primary route of exposure is via the dermal and inhalation routes.

The results of testing with Intrepid 240F Insecticide did not reveal an acute toxicity hazard.

Methoxyfenozide was not demonstrated to be a developmental, reproductive or nervous system toxicant, carcinogen or genotoxicant. In general, the toxicological effects of methoxyfenozide were observed only at relatively high doses with more significant toxicity observed at doses that were greater than or equal to the limit dose. Hematological and liver effects consistently defined the NOAELs in the toxicology database. The dog displayed the greatest sensitivity in relation to blood effects. Shorter-term dosing in this species demonstrated the effects were reversible. Toxicity generally increased with increased duration of dosing.

The NOAEL of 1000 mg/kg bw/day from the 28-day dermal study in the rat was selected as the most appropriate endpoint for conducting a short-term risk dermal assessment, intermittent in nature. The basis for this selection is as follows:

- the route of exposure is relevant to the occupational scenario;
- the duration of study is comparable to the proposed conditions of exposure;
- the study was well conducted and included examination of target tissues of toxicity (liver and blood).

A margin of exposure (MOE) of 100 to account for intraspecies and interspecies variation is considered adequate.

In the absence of repeat-dose inhalation toxicity studies, the results from the extended period of dosing in the 90-day dietary dog study were considered most appropriate for use in the short-term inhalation risk assessment. In that study, animals dosed at 15 ppm (0.6 mg/kg bw/day) for 90 days were administered the test material at a dose of 15 000 ppm (422 and 460 mg/kg bw/day for males and females respectively) for an additional six weeks prior to sacrifice. These animals did not demonstrate any treatment-related effects at the higher dose level, which represents a conservative "NOAEL" for the six-week dosing period. The duration of the dosing at this level (six weeks) is comparable to the proposed conditions of exposure; the study was well conducted and included examination of target tissues of toxicity (liver and blood). An MOE of 100 is considered adequate.

The NOAEL of 198 mg/kg bw/day from the 90-day dietary study in the dog was selected as the most appropriate endpoint for conducting an intermediate-term dermal risk assessment (daily, 2–3 months). The basis for this selection is as follows: the duration of study is comparable to the proposed conditions of exposure; the study was well conducted and included examination of target tissues of toxicity (liver and blood). An MOE of 100 is considered adequate.

Dermal absorption

Dermal absorption is required as an adequate endpoint and since a dermal toxicity study was not submitted for all exposure durations, an estimate was thus required. A dermal absorption value of 8% was selected based on a dermal penetration study submitted by the applicant. Methoxyfenozide in distilled water was applied to the shaved dorsal surface (~10 cm^2) of male rats (three/group) at nominal doses of 250, 25, and 2.5 μg a.i./cm^2 for periods of 1, 10 and 24 hours. Subjects remained exposed until sacrifice. Eight percent dermal absorption was obtained from the low- and medium-dose groups with 10 hour exposure times. This value incorporates both systemic and skin-bound residues, as the study did not demonstrate the fate of skin bound residues over time.

3.5 Impact on human or animal health arising from exposure to the active substance or to impurities contained in it

3.5.1 Occupational exposure and risk

3.5.1.1 Handler exposure and risk

Farmers and custom applicators have potential for exposure to methoxyfenozide during application to apple trees. Only ground application is proposed. Typical areas treated per day are 16 ha with airblast equipment for both farmers and custom applicators. Smaller areas may be treated with handheld equipment. Farmers and custom applicators would

typically be exposed once every 10–14 days, twice during the growing season. There is a potential for intermittent exposure over a short term (4–6 weeks) starting as early as prebloom, and continuing throughout the summer.

Exposure estimates for mixers, loaders and applicators (M/L/As) are based on data from the Pesticide Handlers Exposure Database (PHED). PHED version 1.1 is a compilation of generic M/L/A passive dosimetry data with associated software, which facilitates the generation of scenario-specific exposure estimates. With a few exceptions, the PHED estimates meet criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides. To estimate exposure for each use scenario, appropriate subsets of A and B were created from the all liquid open mixing/loading and open cab airblast database files of PHED. All data were normalized for kg of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part.

The exposure estimates for Intrepid 240F Insecticide were based on mixer and loaders wearing long pants, long-sleeved shirts and waterproof gloves. For applicators, PHED assessments were based on long pants and long-sleeved shirts.

For short-term durations, the dermal exposure estimates for farmers and custom M/L/As were compared to a NOAEL of 1000 mg/kg bw/day from a 28-day dermal study on rats. The inhalation exposure estimates were compared to a NOAEL of 422 mg/kg bw/day from a 90-day dietary dog study. The MOEs were compared to the target MOE of 100 and found to be acceptable. A summary of operator exposure estimates is provided in Table 3.5.1.1.1.

Table 3.5.1.1.1 Daily exposure estimates (µg a.i./kg bw/day) for M/L/A on orchards using airblast equipment

Exposure pattern	Scenario	Daily exposure (µg a.i./kg bw/day)[A]		MOE[C] (Target 100)	
		Dermal deposition[B]	Inhalation	Dermal[D]	Inhalation[E]
Farmers and custom applicators: 5.76 kg a.i./day (360 g a.i./ha × 16 ha)	Mixer/ loader/ applicator	72.36	0.61	**13820**	**693000**

A Calculated as µg a.i./kg a.i. handled × proposed application rate (g a.i./ha) × area treated per day (ha)/body weight (70 kg)

B Dermal absorption data were not required since a dermal toxicity endpoint value was chosen for the risk assessment

C MOE = NOAEL/daily exposure (mg a.i./kg bw/day)

D Based on a NOAEL of 1000 mg/kg bw/day from a 28-day dermal study on rats

E Based on a NOAEL of 422 mg/kg bw/day from a 90-day dietary dog study

3.5.1.2 Post-application exposure and risk

There is a potential for short- to intermediate-term exposure to workers scouting, pruning, hand line irrigating, hand harvesting and thinning apples treated with methoxyfenozide. Exposure estimates were generated by coupling dislodgeable foliar residue (DFR) data with activity specific transfer coefficients. The applicant provided a DFR study to address post-application exposure. Standard defaults were also used to estimate exposure, including the assumption that workers spend 8 hours per day working and each have a body weight of 70 kg. Since the applicant is a member of the Agricultural Re-entry Task Force (ARTF), the transfer coefficients for orchards, based on ARTF data, were used for risk assessment purposes. In addition, a dermal absorption value of 8.0 % was incorporated (from the rat in-vivo dermal absorption study) to estimate the absorbed dose.

Estimates of exposure to individuals who re-enter treated orchards were based on a DFR study, which measured the amount of residue that could be available to workers that come into contact with treated trees. This study was designed to collect data to calculate dislodgeable foliar residue dissipation curves for methoxyfenozide on apple trees at a single test site in Pennsylvania. The geographical and climatic conditions were relevant to Canadian growing regions. This study was conducted according to current methodologies and the design of the study is consistent with acceptable protocols and guidelines. There were 6 applications, 10–14 days apart. DFR samples were collected pre- and post-applications 1, 2 and 6. Samples were also gathered on days 0–32 after the sixth

application. There were a few minor study limitations that did not impact the DFR values obtained from the study. The study was considered acceptable for use in predicting DFR on apples in Canada.

The results indicated that there is minimal decline in methoxyfenozide dislodgeable residues over time. The LOD was not reached 35 days following the sixth application. The most appropriate value to use in a risk assessment is the day 0 value after the sixth application (1.15 $\mu g/cm^2$).

Intermediate-term exposure estimates for workers re-entering treated fields for scouting, irrigating, pruning, hand harvesting, hand line irrigation and thinning, were compared to the NOAEL of 198 mg/kg bw/day from a 90-day dietary dog study. These MOEs were found to be acceptable (>100). A summary of post-application exposure estimates for methoxyfenozide, on the day of last application, are presented in Table 3.5.1.2.1.

Table 3.5.1.2.1 Occupational post-application exposure estimates for methoxyfenozide

Scenario	Transfer coefficient (cm^2/hr)[A]	Absorbed dose (mg/kg bw/day)[B]	MOE[C] (Target 100)
Pruning, scouting	500	0.005	**37700**
Hand line irrigation	1100	0.012	**17100**
Hand harvesting	1500	0.016	**12600**
Thinning	3000	0.032	**6300**

A Transfer coefficients, based on ARTF data.

B Exposure estimates were calculated using the following formula:

$$\frac{\text{DFR 1.15 } (\mu g/cm^2) \times \text{transfer coefficient } (cm^2/hr) \times 8 \text{ hour work day} \times \text{conversion factor (1 mg/1000 } \mu g) \times 8\% \text{ dermal absorption}}{\text{bw (70 kg)}}$$

C MOE = NOAEL of 198 mg/kg bw/day from a 90-day dietary dog study/absorbed dose (mg a.i./kg bw/day)

3.5.2 Residential exposure and risk

3.5.2.1 Handler exposure and risk

There are no domestic products; therefore, a residential handler assessment was not required.

3.5.2.2 Post-application exposure and risk

Residential post-application exposure can occur when adults or youths come into contact with treated foliage while pruning, thinning or hand harvesting treated fruit trees in

residential areas. Although residues on foliage are persistent, the occurrence of exposure activities is infrequent. Therefore, exposure is expected to be of acute to short-term duration. Since there are no acute hazards with methoxyfenozide, an exposure assessment is not necessary.

3.5.3 Bystander exposure and risk

Adults and youth harvesting at pick-your-own operations have the potential for acute exposure to methoxyfenozide residues as this activity is only expected to occur once per year. An acute reference dose was not selected for methoxyfenozide as it is not considered to be acutely toxic; thus, an exposure assessment was not required for the pick-your-own scenario.

3.5.4 Residues relevant to consumer safety

3.5.4.1 Aggregate exposure and risk assessment

Acute dermal exposure from harvesting at pick-your-own facilities or backyard orchards may co-occur with acute dietary exposure. An acute reference dose was not selected for methoxyfenozide as it is not considered to be acutely toxic; thus, an acute aggregate exposure assessment is not required.

4.0 Residues

4.1 Residue summary

4.1.1 Nature of the residue in plants – apples, cotton, grapes and rice

The metabolism of methoxyfenozide in plants was examined in apples, cotton, grapes and rice using a radiolabelled parent. It was labelled at the methoxyphenyl ring (MOP) for apples, the t-butyl moiety (TB) for grapes and at the MOP, TB and dimethylphenyl ring (DMP) for cotton and rice.

Cotton: For the cotton study, two foliar applications of C^{14} labelled parent (labelled at one of the following sites: MOP, TB or DMP) were made to cotton plants at 90 and 120 days after planting at 1.075 kg a.i./ha/application. Thus the total application rate was 2.15 kg a.i./ha for each radiolabelled compound. Immature cotton and boll samples were collected from each of the treatment plots after the first application (90 days after planting), immediately before and after the second application (120 days after planting) and at 7 and 14 days after the second application. Mature bolls and plant samples were harvested 21 days after the second application.

Apples: For the apple study, apple trees were treated with two foliar spray applications of C^{14} labelled parent (labelled at the MOP) made 15 days apart at a rate of 1.008 and 1.064 kg a.i./ha for a total application of 2.072 kg a.i./ha/season. Apples were harvested

immediately after the first application; immediately before and after the second application; and at 0, 7, 14, and 36 days (normal harvest) after the second application.

Grapes: For the grape study, grape vines were treated with two foliar spray applications of C^{14} labelled parent (labelled at the TB) made 28 days apart at a rate of 0.986 and 1.243 kg a.i./ha for a total application of 2.23 kg a.i./ha/season. Grapes and grape foliage were harvested immediately before and after the second application, and at 10, 14, 21, and 27 days (normal harvest) after the second application.

Rice: For the rice study, rice plants were treated with two applications of each C^{14} labelled parent (labelled at DMP, TB or MOP) made 36 days apart. Thus the total application rates were 1.2 kg a.i./ha each for the DMP and TB label applications respectively and 1.06 kg a.i./ha for the MOP label application. For all treatments, the first application was made at the pre-flagleaf stage (30–33 in. in height) and the second was made post-flowering (33–36 in. in height). Rice was harvested at a preharvest interval (PHI) of 62 days.

Based on the results of these studies, fragmentation of the methoxyfenozide molecule was not observed; only whole-molecule metabolites were identified in the submitted studies. The parent compound, methoxyfenozide, was the single major component of the residue in all four studies, comprising 91% of the residue in apples, 80% in grapes, 65–69% in rice, and 46–67% of the residue in cotton. No other single metabolite in any crop occurred at > 10% of the total residue. Small amounts of methoxyfenozide may undergo oxidation to yield minor products, such as B-ring alcohols (RH-131364) or A-ring mono-alcohols (RH-117236). These metabolites may undergo further oxidation to form the B-ring acid RH-131154, glucose conjugate of the B-ring alcohol, glucose conjugate of the A-ring alcohol, or A- and B-ring di-alcohol RH-141511. These may be further oxidized to form the B-ring di-alcohol RH-131157. Some methoxyfenozide may be present in the form of fatty acid conjugates (cotton) and bound residues. Based on these results, for monitoring purposes, the ROC is defined as parent compound in apples, grapes, rice and cotton.

The initial conclusions from the primary metabolism studies were that, although the metabolism of methoxyfenozide in cotton, apples, grapes and rice was qualitatively similar, the results were *quantitatively* dissimilar. This conclusion was based on a temporal comparison of the minor (< 10% TRR) metabolites that were observed in the primary plant metabolism studies. However, the original review of the apple, grape, rice and cotton metabolism studies concluded that the definition of the ROC could not be extended beyond these species. Therefore, any requests for maximum residue limits (MRLs) or for use on crops other than apples, grapes, rice and cotton (or their respective crop groups) will require additional metabolism studies.

4.1.2 Plant metabolism rationale

In order to fulfill the plant metabolism requirements for the current domestic registration on apples, the registrant chose to demonstrate similar metabolism in three diverse crops. In order to do so, the results of the primary crop metabolism studies (discussed above) were examined in conjunction with the confined crop rotation study carried out on various secondary crops (radishes, mustard and wheat) discussed below. Furthermore, new environmental fate data that was submitted in the framework of the current submission was also examined. The new information illustrated that the differences in the extent of the metabolism observed in the various crops was related to the two following factors.

First, the environmental fate data illustrated a difference in half-life for the parent compound in soil and aquatic environments (for example, to the rice growing environment). Based on this new information, the PMRA was able to conclude that the apparent differences observed in the rice metabolism study were likely due to the absorption of novel radiolabelled compounds that were produced during the metabolism of the parent compound and found in the water.

Furthermore, the new environmental information also illustrated a temporal relationship between the extent of metabolism observed in the primary and secondary (rotated) crop studies. Based on this relationship, the PMRA proposed that the more complex metabolism depicted in the rotated crops arose *not* from an inherently different metabolic capacity of these crops, but rather due to the longer timeframes that were followed in these crop metabolism studies compared to the primary crops (33–257 days versus 14–62 days, respectively). By understanding the temporal relationship, the PMRA was able to integrate the metabolic profiles from the two types of studies, which demonstrated that the metabolism of methoxyfenozide in rotated crops is in fact *a continuation of the metabolic processes observed in the primary crops.*

In conclusion, by integrating the results of all of the studies available, the PMRA was able to examine the metabolism of methoxyfenozide *over a much longer period of time.* The outcome demonstrated that the *overall* metabolism of methoxyfenozide is both qualitatively and quantitatively similar in apples, cotton, grapes, rice, mustard, radishes and wheat.

The PMRA can now conclude that the metabolism in all plants is adequately understood and the ROC in plants was defined as the parent compound, methoxyfenozide.

4.1.3 Confined accumulation in rotational crops

The C^{14} parent compound (labelled at either the MOP, TB and DMP) were mixed with ^{13}C-methoxyfenozide and unlabelled methoxyfenozide. Each test substance was then formulated as a 5% emulsifiable concentrate formulation (diluted with water) and applied

to plots of sandy loam soil at a total application rate of 2.24 kg a.i./ha (3 × 0.75 kg a.i./ha/application, 3–4 day retreatment interval). Mustard, radish and winter wheat were planted in the plots at 31, 91 and 364 days after the final treatment. Samples of immature RAC from all crops were collected 33–157 days after planting. Mature radish and mustard was collected at 47–170 days after planting and mature wheat was collected at 226–257 days after planting. In general, residues were highest from the 31-DAT (days after treatment) interval and declined in the subsequent intervals.

In mustard and radish crops, methoxyfenozide, RH-151055 and RH-152067 accounted for the majority of residues and were identified at levels > 0.01 ppm. Based on these results, the PMRA concluded that the ROC in the human edible component of mustard and radish is defined as methoxyfenozide, RH-151055 and RH-152067. In wheat forage and straw fractions (components not edible for humans), RH-151055 and RH-152072 accounted for the majority of residues and were identified at > 0.01 ppm of TRR. However, in wheat grain metabolites RH-117236 and Met G6 were found at levels > 0.01 ppm and > 10% TRR. Since Met G-6 was not fully identified, it will not be included in the ROC for wheat. Based on these results, it was concluded that the ROC for the human edible component of wheat is methoxyfenozide and RH-117236.

4.1.4 Field accumulation in rotational crops

A field accumulation in rotated crops was not required since the current submission is for apples.

4.1.5 Nature of the residue in animals – goats and hens

In the lactating goat metabolism study, methoxyfenozide (radiolabelled at the MOP, TB and DMP) was administered orally to lactating goats at dose levels of 45, 32, and 61 ppm/day for the MOP, DMP and TB labels, respectively once a day for seven consecutive days. The main route of elimination of radioactivity was through the feces and urine (74–84% and 5–7%, respectively). In milk, leg muscle, loin muscle and fat, methoxyfenozide was the predominant residue identified (> 10% TRR): 10.9–35.1% (milk), 24.7% (leg muscle), 19.3–20.3% (loin muscle) and 68.3–82.3% (fat) depending on the label. In liver and kidney, metabolite RH-141518 accounted for the majority of the identified radioactivity (> 10% TRR): 22.9–29.4% (liver) and 24.9–42.3% (kidney) depending on the label. Based on these results, the ROC is defined in milk and tissues of ruminants (except liver and kidney) as the parent compound, methoxyfenozide. In the liver and kidneys of ruminants, the ROC is defined as methoxyfenozide plus the metabolite RH-141518.

In the laying hen metabolism study, methoxyfenozide (radiolabelled at the MOP, TB and DMP) was administered orally to laying hens (total of 44 hens; species and strain not recorded) at dose levels of 58 ppm/day for the MOP label (15 hens); 60 ppm/day for the DMP label (15 hens); and 68 ppm/day for the TB label (14 hens); once a day for seven consecutive days. The main route of elimination of radioactivity was through the excreta

and cage wash (84–93%). The major metabolite identified (> 10% TRR) in the following components, was RH-141518 depending on the label: eggs (26.5–30.3%), liver (15.1–19.3%), kidney (32.6–35.7%) and TB-labelled light muscle (10.11%) and dark muscle (31.0%). The parent compound, methoxyfenozide, was the major compound identified in both fat samples and skin with fat samples with the MOP label (44.0% and 23.11%, respectively) and in dark muscle with the DMP label (10.9%). The parent compound was also identified in eggs, liver and kidney with some of the labels and in light and dark muscle with the TB label. RH-141518 was also identified in all skin samples and all skin with fat samples. Based on these results, the ROC in eggs and tissues of poultry is defined as methoxyfenozide plus the metabolite RH-141518.

The animal metabolism studies were acceptable. Based on the results of the goat and hen studies, the metabolism of methoxyfenozide in animals is considered well understood.

4.1.6 Storage stability data – plant/animals

For plant matrices, the data presented in the freezer storage stability study indicated that residues of methoxyfenozide were stable at -20°C in/on apples (for 365 days), cotton (for 715 days), tomatoes (for 372 days), field corn (for 397 days) and head lettuce (for 365 days).

If a residue can be shown to be stable in five diverse crops, then the residue can be considered to be stable in all other crops. In view of this, these results fully support the apple field samples being stored for 346 days.

For apple processed fractions, storage stability was demonstrated as part of the freezer storage stability study on apple RAC (discussed above). Methoxyfenozide residues were shown to be stable in freezer-stored apples, apple juice and apple pomace for 12 months, 9.4 months and 10 months, respectively. Freezer storage stability data for washed and peeled apples was not available. However, given the minor importance of each of these fractions to a dietary risk assessment, this was not considered a deficiency. Therefore, this data supports the freezer storage interval (from collection to analysis) of samples in the apple processing study where samples were stored for up to 7 months.

For animal matrices, stability of methoxyfenozide and metabolite RH-141518 was assessed in milk and animal matrices. In the study, untreated milk and animal tissues were spiked with methoxyfenozide at 1 ppm and kidney and liver samples were spiked with metabolite RH-141518 at 0.92 ppm. All spiked samples were then stored in the freezer to assess the stability of the residues after freezer storage. Results from the study indicated that residues of methoxyfenozide were stable at -20°C in/on milk (for 3.5 months), cow muscle (for 5.4 months), cow liver (for 8.6 months), and cow kidney (for 8.7 months). Residues of metabolite RH-141518 were stable for the first 5 months in cow kidney, but declined 13–29% after 6–9 months of freezer storage. Similarly, in cow liver, residues of RH-141518 declined by 20–40% after less than one month of freezer

storage, but showed no further decline for up to 9 months. Based on these results, an adjustment factor must be applied to the residue levels found in the kidney and liver samples in the animal feeding study.

4.1.7 Crop field trials

For apples, 12 supervised crop field trials were conducted in the United States and Canada with Intrepid 2F (23.2% methoxyfenozide). Trials were carried out in Zone 1 (one trial), Zone 1A (one trial), Zone 5B (three trials), Zone 5 (four trials) and Zone 11 (three trials). The numbers and locations of the trials are in accordance with Agency requirements. Apples trees were treated with four applications at 0.360 kg a.i./ha/application for a total seasonal application rate of 1.44 kg a.i./ha. Mature apple fruit was harvested as the RAC at a PHI of 14 (±1) days. Residues of methoxyfenozide in/on treated apples from these trials ranged from 0.091–0.587 ppm.

A residue decline trial was also conducted where apples were collected at 1, 3, 7, 14 and 18 days after the last application (DALA). The first three sets of samples (representing 1, 3 and 7 DALA) had unexpectedly low residue levels (0.0227–0.0429 ppm). Apple samples harvested at a PHI of 14 days had a mean residue value of 0.262 ppm, and samples harvested at a PHI of 18 days had a mean residue value of 0.208 ppm. These values showed no significant decrease in residue levels with increasing PHIs.

Currently, an MRL of 1.5 ppm is promulgated for pome fruit based on a previous import MRL submission. The existing MRL will cover the level of expected residues in/on apples treated at the proposed label rate. Residue decline studies on apples also demonstrated that the proposed MRL for apples will not be exceeded when collected at the label PHI of 14 days.

One trial was also carried out as a bridging study to assess any differences in expected residues arising from two formulations of the end-use product Intrepid 80W and Intrepid 2F (methoxyfenozide, 23.2%). The trial consisted of two plots where each plot received six applications of one of the end-use products at 0.340 kg a.i./ha/application for a total seasonal application rate of 2.04 kg a.i./ha. Fruit was harvested from both plots at a PHI of 7 days and analyzed for residues of methoxyfenozide. The mean residue level in/on the treated fruit from the Intrepid 80W plot and the Intrepid 2F plot was 0.545 ppm and 0.498 ppm, respectively. These results demonstrate no significant difference in expected residue levels arising from the different formulations.

4.1.8 Processed food/feed

Two apple processing studies were conducted in which apples were treated at a rate of 2.02 kg a.i./ha with either RH-2485 80WP (80% methoxyfenozide) or RH-2485 2F (23% methoxyfenozide). These rates correspond to rates greater than those on the proposed Canadian label. The treated fruit was then processed into apple juice or wet apple pomace or alternatively, either washed or peeled. Comparison of the level of methoxyfenozide

residues in/on the RAC with those in the corresponding processed fraction resulted in calculated concentration factors of 0.2× for apple juice, 6.0× for wet apple pomace, 1.1× for washed apples and 0.3× for peeled apples. Therefore, the residues expected in/on washed apples, peeled apples and apple juice will be covered by the MRL set on the RAC. Since apple pomace is a livestock feed item, an evaluation of the transfer of methoxyfenozide residues to livestock tissue and milk was assessed in the livestock feeding study.

4.1.9 Meat/Milk/Poultry/Eggs

Lactating cattle (Holstein dairy cattle; 3–4 per dosing level) were administered methoxyfenozide at a rate of 0, 19.5, 59.6, and 192 ppm methoxyfenozide in gelatin capsules for 28 days (0, 415, 1246, and 4154 mg methoxyfenozide/21–22 kg feed, respectively). Based on the domestic use pattern for the current submission (apples), where apple pomace is the only feed item for livestock, the following maximum theoretical dietary burden (MTDB) values were calculated: 1.59 ppm for cattle, 0 ppm for hogs and 0 ppm for poultry. Using these values, residues resulting from the closest feeding level (19.5 ppm) were found to be below the LOQ (< 0.01 ppm) in milk, fat, muscle and kidney of cattle. In liver, combined residues of methoxyfenozide plus RH-141518 ranged from 0.02–0.04 ppm. However, the following considerations were taken when evaluating these results from a regulatory perspective:

- First, the closest feeding level was 12.3× higher (19.5 ppm) than the calculated MTDB value (1.59 ppm).
- Also, the MTDB calculation itself is considerably conservative in nature (100% crop treated, 100% treated crops as feed).
- Also the LOQ of the analytical method for residue analysis in animal matrices is 0.02 ppm.

In view of these considerations, it is not likely that residues of methoxyfenozide will be quantifiable in/on any cattle matrices and, therefore, from a regulatory perspective no action is required in the framework of the current submission.

4.1.10 Dietary risk assessment

Chronic dietary exposure analyses were performed in order to determine the exposure and risk estimates that resulted from the use of methoxyfenozide in Canada and the exposure to crops imported from the United States. The ADI for methoxyfenozide was determined to be 0.1 mg/kg bw/day, based on a NOAEL of 10.2 mg/kg bw/day from a two-year dietary toxicity study in rats and an uncertainty/safety factor of 100. The chronic dietary exposure from all supported methoxyfenozide food uses for the representative population subgroups ranged from 10.2% to 18.7% of the ADI. The currently proposed uses for methoxyfenozide encompass only agricultural use sites. Therefore, when addressing aggregate exposures, only the dietary pathways of food and drinking water were considered (EEC value = 101 µg a.i./L, Level 1; the EEC value was based on the rate initially proposed by the registrant, i.e., four applications at 0.36 kg a.i./ha/application).

Aggregate exposure from food and water was considered acceptable and below the level of concern: 21.8% of the ADI for all children 1–2 years old.

Therefore, the proposed domestic registration of methoxyfenozide on apples does not pose an unacceptable chronic risk (from both food and water) to any segment of the population, including infants, children, adults and seniors.

5.0 Fate and behaviour in the environment

5.1 Physical and chemical properties relevant to the environment

Physical and chemical properties of methoxyfenozide relevant to the environment are presented in Appendix III, Table 1. Methoxyfenozide is classified as having low solubility in water over the range of pH 5 to pH 9, and is not expected to dissociate in water. The vapour pressure and Henry's Law constant indicate that methoxyfenozide is non-volatile under field conditions, from moist soil and water surfaces. Furthermore, methoxyfenozide has a low potential for ultraviolet light-induced phototransformation under normal environmental conditions.

The octanol-water partitioning coefficient indicates that there is potential for the active ingredient to bioconcentrate in organisms.

5.2 Abiotic transformation

In a hydrolysis study, the half-lives of methoxyfenozide were extrapolated to 587, 1572, and 695 d (equivalent to 1.6, 4.3, and 3.7 years) at pHs of 5, 7 and 9, respectively. Thus, methoxyfenozide is stable to hydrolysis at environmentally relevant pHs.

The phototransformation on soil was slow with a half-life of 173 d under conditions of 12 h light:12 h dark. Three minor transformation products were detected on soil: unidentified degradate (0.58% at 14 DAT), RH-131154 (2% at 14 DAT) and RH-117236 (1.5% at 30 DAT). Methoxyfenozide did not phototransform in water under laboratory test conditions of 12 h light:12 h dark. Three minor transformation products were detected in water: RH-131154 (0.6% at 21 DAT), unidentified degradate 2 (0.09% at 3 DAT) and unidentified degradate 3 (0.35% at 30 DAT). Phototransformation would not be a route of transformation of methoxyfenozide on soil or in water. Data on the phototransformation in air is not required due to the lack of volatility.

Therefore, mechanisms of abiotic transformation serve minimally as routes of transformation for methoxyfenozide in the environment.

5.3 Biotransformation

Biotransformation of methoxyfenozide was examined in aerobic loam soil, loamy sand and sandy clay loam soils in three laboratory studies. Methoxyfenozide transformed very

slowly through microbial action, with reported DT_{50} values of 336 to 1100 d. Consequently, methoxyfenozide is classified as persistent in aerobic soils (Appendix III, Table 2). Six minor transformation products were detected: RH-113154, formed at maximum levels of 1 to 3.2% of the applied radioactivity, and five unidentified transformation products. Total CO_2 production over the duration of the studies ranged from 2 to 5.5% of applied radioactivity.

Methoxyfenozide is persistent under aerobic water/sediment conditions, with a reported DT_{50} of 387 to 963 d. The major transformation product formed was RH-117236, which reached a maximum of 12.6% at 91 DAT, but was not persistent. RH-117236 decreased to 3% by 365 DAT. Less than 6% of the applied dose was detected as CO_2.

In an anaerobic water/sediment system, methoxyfenozide was persistent, with a reported DT_{50} of 654 d. The minor transformation product RH-131154 appeared at about 2% of the applied dose. Total CO_2 production over the duration of the study was 3.2%.

The reported DT_{50}s for biotransformation in aerobic soil, aerobic water/sediment, and anaerobic water/sediment do not account for unextracted radioactivity. Thus, actual biotransformation DT_{50}s incorporating bound residues may be longer than these reported values.

Therefore, mechanisms of biotic transformation are not an important route of transformation.

5.4 Mobility

The adsorption/desorption characteristics of methoxyfenozide were studied in five soil types from the United States. After 20–24 h of equilibration, the adsorption K_{oc} values were 267 for loam soil, 678–922 for loamy sand soil, 219 for sandy loam soil, and 365 for silt loam soil. The following K_{oc} values were determined using four soils from Germany (after 24 hours of equilibration): 200.2 for loamy sand soil, 314.1 for silt loam soil, 330.6 for sandy loam soil, and 318.4 for silty clay soil (Appendix III, Table 2). Based on these results, methoxyfenozide is classified as moderately mobile in loam, sandy loam, silt loam, and silty clay soils, and has low to moderate mobility in loamy sand soil.

5.5 Dissipation and accumulation under field conditions

In Canadian field studies of terrestrial dissipation, DT_{50}s ranged from 239 to 433 d in loam, silt loam, and fine sandy loam soils. At a relevant American site, the DT_{50} was 268 d in sandy soil. These studies indicate that methoxyfenozide is persistent in these soils (Appendix III, Table 2), and that there is a high potential for carryover. The results from these field studies indicated that approximately 50% of applied methoxyfenozide is expected to carryover into the next growing season, and 94% of the yearly application rate will be found after 4 years of continuous use.

5.6 Bioconcentration

In a bioconcentration study, bluegill sunfish (*Lepomis macrochirus*) were exposed to radiolabelled methoxyfenozide (RH-2485) at a nominal flow-through water concentration of 0.20 mg a.i./L and 0.02 mg a.i./L for 28 days, followed by 14 days of depuration.

The uptake rate constant (K_1), depuration rate constant (K_2), time to 50% clearance and steady-state bioconcentration factor (BCF) for whole fish were determined using the BIOFAC computer program. Including the parent chemical, 25 metabolites were detected. The parent chemical accounted for up to 12.6% of that applied in viscera and 46% in fillet. Major metabolites included M3 to M6. The study author reported that the data and all parameters measured from both the 0.2 mg a.i./L and 0.02 mg a.i./L water concentration experiments indicated that the kinetic behaviour of methoxyfenozide in fish is independent of test substance concentration. Daily BCF for both concentrations ranged from 0.8 to 1.3 in fillet; 4.7 to 11.0 in whole fish; and 8.9 to 23 in viscera. The mean whole fish BCF was determined to be 8.8 to 8.9.

Methoxyfenozide showed very little bioconcentration in fish based on the present 28-day study using bluegill sunfish. The highest mean BCF recorded was 8.9–23 in viscera and the mean BCF in whole fish was 8.9. The depuration half-life was less than half a day, while the 90% clearance time (T_{90}) was < 1 d. These results indicate rapid elimination of methoxyfenozide from fish tissue.

5.7 Summary of fate and behaviour in the terrestrial environment

A summary of fate and behaviour of methoxyfenozide in the terrestrial environment is presented in Appendix III, Table 2. Methoxyfenozide is persistent in soil, is moderately mobile, and will accumulate in the environment following repeated applications. Hydrolysis would not be an important route of transformation in the environment. Methoxyfenozide is not likely to volatilize from moist soil and water surfaces, given its low vapour pressure and low Henry's Law constant. Methoxyfenozide undergoes very limited phototransformation on soil with three minor transformation products produced from these processes. Therefore, while subject to mechanisms of abiotic transformation, these processes would not predominate in the environment. Methoxyfenozide degrades very slowly by microbial actions. The results of three laboratory studies of soil biotransformation processes demonstrated that methoxyfenozide is persistent in aerobic soils, with reported DT_{50} values of 336–1100 d. These DT_{50}s reflect not only metabolic processes, but also "losses" due to unextracted radioactivity; thus, actual metabolic DT_{50}s may be longer than these reported values. No major transformation products were detected in aerobic soils. In Canadian field studies of terrestrial dissipation, DT_{50}s ranged from 239–433 d in soils and in a relevant American study, the DT_{50} was 268 d, indicating that methoxyfenozide is persistent in soil. Based on the laboratory results of absorption/desorption, methoxyfenozide is classified as low to moderately mobile in soil. Due to its resistance to degradation and mobility, methoxyfenozide has the potential to accumulate and move off the site of application by leaching and erosion/runoff.

5.8 Summary of fate and behaviour in the aquatic environment

A summary of fate and behaviour of methoxyfenozide in the aquatic environment is presented in Appendix III, Table 3. Methoxyfenozide is stable with respect to transformation by hydrolysis. Phototransformation will not be a route of transformation of methoxyfenozide in water. Laboratory studies of aquatic biotransformation demonstrated that methoxyfenozide was persistent under both aerobic and anaerobic conditions and it partitions to and accumulates in sediment. Although dissipation times for sediment were not presented, the DT_{50}s for water-sediment systems were 387–963 d. Based on the information submitted, the primary fate of methoxyfenozide in aquatic systems is partitioning to sediment where methoxyfenozide persists. Based on its log K_{ow} value of 3.72, methoxyfenozide has a potential for bioconcentration, thus the kinetics of uptake and elimination of ^{14}C-methoxyfenozide in the bluegill sunfish were studied. Methoxyfenozide showed very little bioconcentration in fish. The highest mean BCF recorded was 8.9–23 in viscera and the mean BCF in whole fish was 8.9. The depuration half-life was less than half a day, while the 90% clearance time (T_{90}) was < 1 d. These results indicate rapid elimination of methoxyfenozide from fish tissue, contrary to the potential for bioconcentration indicated by the log K_{ow} value.

5.9 Expected environmental concentrations

The expected environmental concentrations (EEC) of methoxyfenozide in environmental compartments of concern were estimated based on calculations made using standard scenarios. These concentrations are used as initial approximations for estimating the potential exposure to wildlife. The EECs were determined for methoxyfenozide applied at the maximum rate of 2 applications at 240 g a.i./ha (480 g a.i./ha year) for apples, with a 10-day interval between applications. The scenario assumes that the concentrations in the various compartments were obtained immediately following the second application.

5.9.1 Soil

The EEC of methoxyfenozide in soil was calculated assuming application to bare soil, a soil bulk density of 1.5 g/cm^3, a soil depth of 15 cm, and a DT_{50} in soil of 433 days. Based on the maximum annual application rate, the EEC in soil was estimated to be 0.21 mg a.i./kg soil dry weight.

5.9.2 Aquatic systems

5.9.2.1 Ecosystem water

The EEC of methoxyfenozide in water was calculated based on direct overspray, a half-life in water of 962 days, a water density of 1 g/mL and a water depth of 30 cm. Based on the maximum annual application rate, the EEC of methoxyfenozide in water was estimated to be 0.16 mg a.i./L.

5.9.2.2 Drinking water

Concentrations of methoxyfenozide in potential drinking water sources (groundwater and surface water) were estimated in a Level 1 assessment using computer simulation models. The major inputs used in the model reflected the characteristics of sites typical of apple growing regions, application information and environmental fate characteristics.

EECs of methoxyfenozide in groundwater were calculated using the LEACHM model, which simulates leaching through a layered soil profile over a 20-year period. The concentrations calculated using LEACHM are estimates of the flux, or movement, of pesticide into shallow groundwater with time. EECs of methoxyfenozide in surface water (reservoir) were calculated using the PRZM/EXAMS models (over 57 years), which simulate pesticide runoff from a treated field into an adjacent water body and the fate of a pesticide within that water body.

Level 1 drinking water EECs were calculated by the models. In groundwater, the 90th percentile of the daily and yearly averages represents acute and chronic exposure, respectively. In surface water, the 90th percentile of the yearly peak and the yearly average represents acute and chronic exposure, respectively. The modelling results from the Level 1 screening estimate surface water EECs to be 23.2 μg a.i./L (acute) and 6.8 μg a.i./L (chronic); and groundwater EECs to be 35.8 μg a.i./L (acute) and 35.1 μg a.i./L (chronic).

The results from LEACHM indicate that in a more humid climate (e.g., Eastern Canada), methoxyfenozide is expected to reach detectable concentrations in shallow groundwater (e.g., 5 m or less) within 1–2 years.

5.9.3 Vegetation and other food sources

Wild birds and mammals could be exposed to residues of methoxyfenozide as a result of the consumption of sprayed vegetation and/or contaminated prey. Concentrations of methoxyfenozide in the diets of birds and mammals were calculated based on the EECs in vegetation and insects estimated using a nomogram developed by the USEPA from the data of Hoerger and Kenaga (1972) and Kenaga (1973) (see Appendix III, tables 4 and 5). These calculations assumed a direct overspray, no transformation, no interception and a maximum annual rate of 480 g a.i./ha.

However, the turf was mowed (i.e., disturbed) resulting in uncertainty about the accuracy of methoxyfenozide residues obtained (6.3 mg a.i/kg soil from day 15 of the study, the highest residue concentration for turf). Therefore, the PMRA used the nomogram approach to estimate the EECs in the short-range grass.

Methoxyfenozide residues were measured in turf as part of the Canadian field dissipation study. Concentrations were < 2.0% of measured concentrations predicted by the nomogram estimation for short-range grass (340 mg a.i./kg dw).

The diet of bobwhite quail consists of approximately 30% small insects, 15% forage crops and 55% grain. The EEC of methoxyfenozide in the diet of the bobwhite quail is 84 mg a.i./kg dry weight. For mallard ducks, the diet consists of approximately 30% large insects and 70% grain. The EEC of methoxyfenozide in the diet of the mallard duck is 16.2 mg a.i./kg dry weight. These EECs were used in the risk assessment for avian species.

The diet of the rat consists of approximately 70% short grass, 20% grain/seeds, and 10% large insects. The EEC of methoxyfenozide in the diet of the rat is 242 mg a.i./kg dry weight. For mice, the diet consists of approximately 25% short grass, 50% grain/seeds, and 25% leaves/leafy crops. The EEC in the diet of the mouse is 241 mg a.i./kg dry weight. These EECs were used in risk assessment for wild mammal species.

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

The effects on terrestrial organisms are presented in Appendix III, Table 6. The toxicity of methoxyfenozide was studied with earthworms, honeybees, and predatory and parasitic insects.

Earthworms: Methoxyfenozide had no significant effect on earthworm survival at any concentration tested; thus, methoxyfenozide is considered to be non-toxic to earthworms up to a concentration of 1213 mg a.i./kg dw substrate.

Honeybees: There were no compound-related effects in the acute contact or acute oral studies with honeybees. The LC_{50} for both studies (>100 μg a.i./bee) is equivalent to an application rate of 112 kg a.i./ha, which exceeds the proposed single application of 240 g a.i./ha by more than 467 times. Methoxyfenozide is thus classified as relatively non-toxic to honeybees.

Predatory and parasitic insects: Data submitted on the toxicity to beneficial predators and parasites suggested that methoxyfenozide is slightly toxic. The concentrations tested were less than the maximum annual application rate of 480 g a.i./ha (2 applications of 240 g a.i./ha), and effects were observed in some studies conducted at 42% of the maximum annual application rate; therefore, effects on beneficial predators and parasites at the proposed application rate are not known.

Birds: The acute oral 14-day LD_{50} and no observed effect level (NOEL), based on survival of bobwhite quail, were > 2250 and 2250 mg a.i./kg bw, respectively. No chronic oral studies were conducted with the mallard duck. The 5-day dietary LC_{50} and no observed effect concentration (NOEC) of methoxyfenozide to bobwhite quail were > 5620 and 5620 mg a.i./kg diet, respectively. Although no overt signs of toxicity were observed, biologically significant reductions in growth (bw gain) and food consumption were found at 1000 mg a.i./kg diet or greater. This was attributed to a decrease in

palatability of the treated diet. The 5-day dietary LC_{50} and NOEC, based on body weight and food consumption for mallard ducks were > 5620 and 562 mg a.i./kg diet, respectively. Based on the USEPA classification scheme (1985a,b), methoxyfenozide is classified as practically non-toxic to the bobwhite quail and mallard duck. In the reproduction toxicity study, the NOEC of methoxyfenozide to mallard ducks was 780 mg a.i./kg diet, based on mean food consumption and hatchling weight, when compared to the control. The LOEC was 1 000 mg a.i./kg diet, the highest concentration tested. A reproduction toxicity study was submitted for the bobwhite quail. The study was unacceptable based on the lack of determinable NOEC values. The study did, however, indicate eggshell thinning at low doses.

Wild mammals: The effects on mammals are presented in Section 3.0 and Appendix I. The acute toxicity of methoxyfenozide to mammals was low (rat LD_{50} > 5000 mg a.i./kg bw). The lowest NOEC values for subchronic or chronic dietary exposure were 200 mg a.i./kg diet (2-year rat) and 7000 mg a.i./kg diet (90-day mouse). These studies indicate that, generally, the toxicological effects of methoxyfenozide are observed only at relatively high doses (in many studies, effects were observed only at doses greater than or equal to the limit dose) and that toxicity increased with increased duration of dosing (rats, dogs). Alterations in hematological parameters (decreased RBC counts, hemoglobin and hematocrit, increased methemoglobin, and increased platelets), increases in bilirubin levels as well as effects on the liver (periportal hepatocellular hypertrophy, increased liver weight), thyroid (hypertrophy, altered colloid) and adrenals (increased weight) were the most significant effects reported. Methoxyfenozide was not a developmental, reproductive or nervous system toxicant. Study results did not indicate that young animals were more sensitive to the effects of methoxyfenozide than adults. Effects on endocrine organs (thyroid and adrenals) were observed at relatively high doses only.

6.2 Effects on aquatic organisms

The effects of methoxyfenozide on aquatic organisms are presented in Appendix III, Table 7.

6.2.1 Freshwater

Daphnia: The acute 48-hour EC_{50} and NOEC, based on immobilization of *Daphnia magna*, were > 3.3 (limit of solubility) and 1.7 mg a.i./L, respectively. Based on the USEPA classification scheme (1985c), methoxyfenozide would be classified as moderately toxic to *Daphnia magna*. The 21-day chronic EC_{50} and NOEC based on survival, reproduction, and growth were 0.39 and 0.20 mg a.i./L, respectively.

Chironomid: Two chronic studies were conducted with the sediment dwelling stage of the midge (*Chironomus riparius*), one with methoxyfenozide and the second with the transformation product RH-117236. The EC_{50} and NOEC based on emergence and development were 0.014 and 0.0065 mg a.i./L, respectively. The NOEC based on emergence for the transformation product was < 0.1 mg RH-117236/L.

Fish: The acute 96-hour LC_{50} and NOEC of methoxyfenozide to rainbow trout and bluegill sunfish were both > 3.3 and 3.3 mg a.i./L (limit of solubility in water), respectively. Based on the USEPA classification scheme (1985d), methoxyfenozide is classified as moderately toxic to rainbow trout and bluegill sunfish. The 262-day chronic LC_{50}, NOEC and LOEC of methoxyfenozide to fathead minnow based on F1 survival (56 day post-hatch) were > 3.3, 0.53 and 1.0 mg a.i./L, respectively.

The most sensitive freshwater aquatic toxicity endpoint was the 28-day NOEC (0.0065 mg a.i./L) for chironomids.

6.2.2 Marine

Mysid shrimp: The acute 96-hour LC_{50} and NOEC based on the survival of *Mysidopsis bahia* were 1.3 and 0.68 mg a.i./L, respectively. Based on the USEPA classification scheme (1985e), methoxyfenozide is classified as moderately toxic to mysid shrimp. The 37-day chronic LOEC and NOEC based on survival were 100 and 51 μg a.i./L, respectively.

Eastern oyster: The chronic 96-hour EC_{50} and NOEC based on shell deposition were 1.2 and 0.4 mg a.i./L, respectively. Shell growth inhibition in the treatments ranged from 4.7 to 82%. Based on the USEPA classification scheme (1985e), methoxyfenozide would be classified as moderately toxic to the eastern oyster.

Fish: The acute 96-hour LC_{50} and NOEC based on survival of sheepshead minnow were > 2.8 and 2.8 mg a.i./L, respectively; thus, methoxyfenozide would be classified as moderately toxic to sheepshead minnow (USEPA 1985e).

6.3 Effects on biological methods of sewage treatment

Not applicable for the proposed use.

6.4 Risk characterization

Risk assessment integrates the exposure and ecotoxicology data to estimate the potential for adverse ecological effects. The PMRA currently conducts a deterministic environmental risk assessment of pest control products. Environmental risk is characterized using the risk quotient (RQ), which is the ratio of the EEC to the toxicity endpoint. The endpoint used for both acute and chronic toxicity is the NOEC from the appropriate laboratory study. In those cases for which a NOEC was not reported, the value was estimated as $0.1 \times LD_{50}$ or $0.1 \times LC_{50}$.

6.4.1 Environmental behaviour

Methoxyfenozide is persistent in soil, water and sediment. Approximately 50% of methoxyfenozide is expected to carryover into the next growing season. From the results

of the field study, it is estimated that 94% of the yearly application rate will be present after four years of continuous use. In addition to acute exposure, there is, a potential for prolonged exposure of soil- and sediment-dwelling organisms to methoxyfenozide residues. Exposure of wild birds and mammals can be expected from the consumption of contaminated vegetation. Methoxyfenozide may enter the aquatic environment through spray drift from orchard airblast application and/or runoff via sorption to soil particles, leaching and movement through tile drainage systems. Therefore, there is a potential for exposure of methoxyfenozide to non-target terrestrial and aquatic organisms. Based on the physicochemical properties of methoxyfenozide, volatilization is not an expected route of exposure to non-target organisms.

6.4.2 Terrestrial organisms

The risk of methoxyfenozide to terrestrial organisms is presented in Appendix III, Table 8.

6.4.2.1 Earthworms

The earthworm acute NOEC was 1213 mg a.i./kg dw substrate. The maximum EEC of methoxyfenozide in soil (0.21 mg a.i./kg) is below the NOEC. The risk quotient is 0.0002; therefore, methoxyfenozide will pose a negligible risk to earthworms.

6.4.2.2 Bees

In both the acute oral and acute contact studies, the LD_{50} for honeybees was > 100 μg a.i./bee, which is equivalent to 112 kg a.i./ha. Two applications of 240 g a.i./ha per year is lower than the LD_{50}. The RQ is 0.3; therefore, methoxyfenozide will not pose any appreciable acute risk to honeybees by oral or contact routes of exposure. The risk to honeybee brood is unknown.

6.4.2.3 Other arthropod species

Non-target arthropods are likely to be exposed to formulated methoxyfenozide by direct spray, and contact with fresh or dry residues. Studies on the toxicity of the active ingredient to beneficial arthropods (butterflies, collembola), predators and parasites at the maximum annual application rate were not submitted; therefore, the risk is unknown.

6.4.2.4 Birds

The EEC of methoxyfenozide in the diets of the bobwhite quail and mallard duck are 84 and 16.2 mg a.i./kg dw, respectively. Individual risk assessments were carried out for acute oral exposure to bobwhite quail, acute dietary exposure to bobwhite quail and mallard duck, and chronic exposure for reproductive effects with mallard duck.

In an acute oral study with bobwhite quail, the LC_{50} was > 2250 mg a.i./kg bw while the NOEL was 2250 mg a.i./kg bw. The average body weight per individual (BWI) of the control group in the study was 0.193 kg bw/ind and the food consumption (FC) was 0.027 kg dw/ind/d. Therefore, the daily intake of methoxyfenozide (DI = FC × EEC) was 2.3 mg a.i./ind/d. Expressed on a per individual basis, the $LD_{50\ (ind)}$ and $NOEL_{(ind)}$ were > 434 and 434 mg a.i./ind, respectively. Based on the predicted daily intake and the $NOEL_{(ind)}$, the maximum number of days of intake of methoxyfenozide by a wild bobwhite quail, equivalent to the dose administered by gavage that had no-observable effect on the laboratory population is 189 days. These values indicate that the application of methoxyfenozide at the maximum proposed label rate will not pose any appreciable risk to wild bird populations, such as the bobwhite quail, that are acutely exposed to methoxyfenozide.

The 14-day LC_{50}s from dietary studies with bobwhite quail and mallard duck were both > 5620 mg a.i./kg diet. The NOECs based on body weight and food consumption were 5620 and 562 mg a.i./kg dw diet for bobwhite quail and mallard duck, respectively. As the EECs in the diet of the bobwhite quail and the mallard duck are expected to be 84 mg a.i./kg dw and 16.2 mg a.i./kg dw, respectively, the risk for bobwhite quail and mallard duck are 0.01 and 0.03, respectively. Thus, methoxyfenozide is considered to pose a negligible dietary risk to bobwhite quails and mallard ducks at the proposed maximum application rate.

A chronic study was submitted that examined reproductive effects in mallard duck. For the mallard duck, the NOEC based on hatchling body weight was 780 mg a.i./kg diet. The NOEC exceeds the EEC in the diet of 16.2 mg a.i./kg diet, resulting in a risk quotient of 0.02. The risk quotient indicates negligible risk to the mallard duck following long-term dietary exposure to methoxyfenozide. Reproductive effects for bobwhite quail are unknown.

6.4.2.5 Wild mammals

The EECs of methoxyfenozide in the diets of rats and mice were 242 and 241 mg a.i./kg dry weight, respectively.

For rats, a body weight per individual (BWI) of 0.35 kg bw/individual and a food consumption (FC) of 0.06 kg dry weight per individual rat was used. Therefore, the daily intake (DI = FC × EEC) of methoxyfenozide is 14.5 mg a.i./ind/d. Two acute oral toxicity studies were reviewed: one for the active ingredient and one for the formulated end-use product. The LD_{50}s in these studies were > 5000 mg a.i./kg bw and > 5000 mg EP/kg dw. Expressed on a per individual basis, the $LD_{50\ (ind)}$s (LD_{50} × BWI) are 1750 mg a.i./ind and 1750 mg EP/ind. As NOECs were not available for either study, one-tenth of the LD_{50} was used as the NOEC. The calculated NOECs are 500 mg a.i./kg bw and 500 mg EP/kg bw, respectively. The $NOEC_{(ind)}$s (NOEC × BWI) are 175 mg a.i./ind for both the active ingredient and end-use product.

From studies with the active ingredient and the end-use product, the maximum number of days of intake by a wild rat to attain a dose equivalent to that administered by gavage in the laboratory having no-observable effect on the laboratory population is 12 days.

For mice, three acute oral toxicity studies were reviewed. Using a hypothetical body weight per individual (BWI) of 0.033 kg bw/ind and a food consumption rate (FC) of 0.006 kg dw/ind mouse per day, the daily intake (DI = FC × EEC) of methoxyfenozide is 1.4 mg a.i./ind/d. The LD_{50}s in these studies were > 5000 mg a.i./kg bw for the active ingredient, > 5000 mg EP/kg bw for the end-use product, and > 5000 mg RH-117236/kg bw for the transformation product. When expressed on a per individual basis, the $LD_{50\,(ind)}$ (LD_{50} × BWI) is 165 mg a.i./ind, 165 mg EP/ind and 165 mg RH-117236/kg bw. Since the NOEL was not reported, one-tenth of the LD_{50} was used in the risk assessment of the acute toxicity to mice. The calculated NOEL is, therefore, 500 mg a.i./kg bw, and the $NOEL_{(ind)}$ (NOEL × BWI) is 16.5 mg a.i./ind, 16.5 mg EP/ind, and 16.5 mg RH-117236/ind. Therefore, the maximum number of days of intake of methoxyfenozide, the end-use product or the transformation product by a wild mouse to attain a dose equivalent to that administered by gavage in the laboratory having no-observable effect on the laboratory population is 12 days.

Based on the above assessments, application of methoxyfenozide in the end-use product at the maximum proposed label rate will pose a negligible acute risk to populations of wild mammals that are exposed to methoxyfenozide on vegetation in their diet (on an acute basis). Furthermore, the transformation product RH-117236 is not expected to pose an acute risk to wild mammals.

In the dietary studies conducted with methoxyfenozide technical on male and female rats, the most sensitive NOEC based on mortality was 200 mg a.i./kg diet (two-year study, male rats). The risk quotient is 1.2, which indicates a moderate dietary risk to rats.

A similar assessment was performed for the dietary studies with male and female mice. The most sensitive NOEC based on mortality was 7000 mg a.i./kg diet for both male and female mice (three-month study, male mice). The risk is 0.03, which indicates a negligible dietary risk to mice.

From reproductive studies with rats, there were parental systemic effects observed. The most sensitive NOEC based on liver weights and body weight gain was 2000 mg a.i./kg dw (for both male and females); however, there were no reproductive effects in multigeneration animals, at the highest concentrations tested. The reproductive studies indicate a low risk to multigeneration offspring.

Based on the studies with rats and mice, methoxyfenozide is expected to pose a negligible reproductive risk, and a moderate long-term dietary risk to wild mammals.

6.4.2.6 Terrestrial plants

Data are not required.

6.4.2.7 Summary of risk to terrestrial organisms

An assessment of the environmental risk associated with the use of methoxyfenozide has identified some areas of concern for terrestrial organisms. Methoxyfenozide poses negligible acute risk to earthworms and honeybees (oral and contact). The risk to honeybee brood is unknown. As a result of the absence of data at the maximum annual field application rate, the risks to beneficial predatory and parasitic insects cannot be determined at this time. Methoxyfenozide poses negligible acute and short-term dietary risk to both birds and wild mammals, but poses a moderate long-term dietary risk to mammals. Based on chronic exposure, methoxyfenozide poses negligible reproductive risk to mallard ducks, and small wild mammals based on the results of the rat laboratory study.

6.4.3 Aquatic organisms

The risk of methoxyfenozide to aquatic organisms is presented in Appendix III, Table 9.

6.4.3.1 Freshwater aquatic organisms

6.4.3.1.1 Invertebrates

Lentic: The acute 48-hour and chronic 21-day NOECs based on the survival of *Daphnia magna* were 1.7 and 0.20 mg a.i./L, respectively. Based on the EEC of methoxyfenozide (0.16 mg a.i./L), there is negligible risk to daphnid on an acute basis (RQ=0.09), and low risk based on chronic exposure (RQ=0.8).

Benthic: The most sensitive endpoint was the 28-day NOEC for the emergence rate of midge larvae (*Chironomus riparius*). The NOEC values based on mean measured concentrations in overlying water on day 0, and in pore water on day 28 were 0.0065 and 0.0026 mg a.i./L, respectively. Based on the EEC in water (0.16 mg a.i./L), the risk quotients ranged from 62 to 25, respectively. Based on these results and the persistence of methoxyfenozide in sediment, methoxyfenozide poses a high risk to chironomids. The transformation product, RH-117236, is approximately 10% of the parent compound at 30 days; therefore, the EEC for RH-117236 was approximately 0.016 mg/L. Based on the EEC and 28 day NOEC (<0.1 mg/L), RH-117236 poses a low chronic risk to chironomids.

Chironomid larvae belong to the Order Diptera. Their trophic diversity and numerical abundance make Diptera an important component in aquatic ecosystems. Diptera function as both primary consumers and as a food resource for other invertebrates (e.g. daphnid), fish, amphibians, reptiles, birds and mammals. Chironomids, which are often the most

abundant organism in both number and biomass, can be particularly significant in ecosystem functioning (Merritt and Cummins 1996). Aquatic insects are important in ecosystem-level monitoring because they are essential components of most ecosystems and they are sensitive indicators of ecosystem deterioration (Reice and Wohlenberg 1993). Other organisms, such as crayfish and frog tadpoles, are also sensitive to aquatic contaminants. Aquatic community level effects of methoxyfenozide are unknown.

6.4.3.1.2 Fish

The most sensitive chronic endpoint was the NOEC (3.3 mg a.i./L) for the survival of rainbow trout and bluegill sunfish. Based on the EEC (0.16 mg a.i./L), methoxyfenozide poses a negligible risk (RQ=0.04) to freshwater fresh on an chronic basis.

The most sensitive chronic endpoint was the NOEC (0.53 mg a.i./L) for survival of F1s in whole life-cycle toxicity to fathead minnow (*Pimephales promelas*). Endpoints affected included those for survival of the F1 generation, the mean number of spawning days, the number of spawns and the number of eggs per spawn in the parental generation. Based on the EEC (0.16 mg a.i./L), methoxyfenozide poses a low chronic risk (RQ=0.3) to the fathead minnow.

6.4.3.2 Marine aquatic organisms

6.4.3.2.1 Invertebrates

The most sensitive acute endpoint is the 96-hour NOEC (0.40 mg a.i./L), based on shell deposition, for the Eastern oyster (*Crassostrea virginica*). Based on the EEC (0.16 mg a.i./L), methoxyfenozide poses a low acute risk (RQ=0.4) to the Eastern oyster.

The most sensitive chronic endpoint is the 37-day NOEC (0.051 mg a.i./L), based on growth effects at low levels in mysid shrimp (*Mysidopsis bahia*), a pelagic marine crustacean. Based on the EEC (0.16 mg a.i./L), methoxyfenozide poses a moderate chronic risk (RQ=3.1) to mysid shrimp.

6.4.3.2.2 Fish

The acute NOEC for Sheepshead minnow is 2.8 mg a.i./L. Based on the EEC (0.16 mg a.i./L), methoxyfenozide poses a negligible acute risk to marine fish.

As with freshwater organisms, the results for mysids and molluscs cannot be generalized to all marine invertebrates as methoxyfenozide partitions to sediment where it accumulates, which is where benthic species will be exposed.

6.4.3.2.3 Algae

6.4.3.2.3.1 Freshwater algae

Data are not required.

6.4.3.2.3.2 Marine algae

Data are not required.

6.4.3.5 Summary of risk to aquatic organisms

An assessment of the environmental risk associated with the use of methoxyfenozide has identified areas of concern for aquatic organisms. For freshwater species, methoxyfenozide poses negligible chronic risk to *Daphnia*, rainbow trout and bluegill sunfish; a low acute risk to *Daphnia* and fathead minnow; and a high chronic risk to chironomid. For marine species, methoxyfenozide poses a negligible acute risk to sheepshead minnow; low acute risk to mysid shrimp and Eastern oyster; and a moderate chronic risk to mysid shrimp. These data demonstrate that the effects of methoxyfenozide are not limited to lepidopteran larvae, but instead, they affect a broad range of non-target aquatic organisms.

6.5 Risk mitigation

Environmental concerns

Application of methoxyfenozide using two applications of 240 g a.i./ha per year (annual rate of 480 g a.i./ha/year) will pose a high risk to chironomids, a moderate risk to marine crustaceans (mysid) and a moderate long-term risk to small mammals. Risks to honeybee broods, predators and parasite as well as bobwhite quail reproduction are unknown at the proposed application rate. Marine bivalve bioaccumulation and long-term community level effects to aquatic organisms are also unknown.

Methoxyfenozide is an ecdysone agonist; and is, therefore, an endocrine disruptor to insects and crustaceans. The persistence, mobility and high carryover of methoxyfenozide, coupled with its mode of action is cause for some level of concern, particularly if this compound enters widespread use. Compounds exhibiting both persistence and endocrine disrupting effects may result in cumulative toxicological effects.

Methoxyfenozide is persistent, and the carryover of residues to subsequent growing seasons is expected (50% to next season; approximately 94% after 4 years of consecutive use). Methoxyfenozide is expected to reach detectable concentrations in shallow groundwater (e.g., 5 m or less) within one to two years, and surface water bodies important for groundwater recharge.

Label statements

To mitigate risks to aquatic organisms and small mammals, the following buffer zones and precautionary label statements will be required.

Under the general heading "ENVIRONMENTAL HAZARDS":

> "This product is toxic to aquatic organisms.
>
> Methoxyfenozide is **persistent and will carryover**; it is recommended that the product, Intrepid 240F Insecticide containing methoxyfenozide, not be used in areas treated with this product during the previous season.
>
> To reduce runoff from treated areas into aquatic habitats, consider the characteristics/conditions of the site before treatment. Site characteristics/conditions that may lead to runoff include, but are not limited to, heavy rainfall, moderate to steep slope, bare soil and poorly draining soil (e.g., soils that are compacted, fine textured or low in organic matter). It is recommended that this product not be applied when heavy rain is forecast. Potential for contamination of aquatic areas as a result of runoff may be reduced by inclusion of a vegetative strip between the treated area and the edge of the water body.
>
> This chemical demonstrates the properties and characteristics associated with chemicals detected in groundwater. The use of this chemical may result in contamination of groundwater particularly in areas where soils are permeable and/or the water table is shallow.
>
> HARMFUL to certain beneficial arthropods. Minimize spray drift to reduce effects on beneficial insects in habitats adjacent to the application site, such as hedgerows and woodland."

Under "GENERAL USE PRECAUTIONS":

> "DO NOT contaminate irrigation/drinking water supplies or aquatic habitats by cleaning equipment or disposing of wastes."

Under "DIRECTIONS FOR USE":

> "DO NOT apply directly to aquatic habitats (such as lakes, rivers, sloughs, ponds, coulees, prairie potholes, creeks, marshes, streams, reservoirs, ditches and wetlands) and estuarine/marine habitats.
>
> **DO NOT** apply during periods of dead calm or when winds are gusty.

Airblast application: **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment area on the upwind side.

DO NOT apply by air.

Buffer zones
The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, coulees, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats."

Method of application	Crop	Buffer zone (m) required to protection	
		Freshwater habitats	Estuarine/marine habitats
Airblast sprayer	Apple	10	5

Data gaps
Due to the PMRA's concerns about the persistence of methoxyfenozide (in soil, water, sediments), its high carryover of residues, moderate mobility and toxicity to non-target organisms, the following additional studies are required:

- Terrestrial arthropods (predators, parasites and collembola)
- Honeybee brood
- Sediment toxicity test with *Hexagenia*
- Bioconcentration using saltwater bivalve molluscs
- Frog embryo teratogenesis assay – *Xenopus* (FETAX)
- Developmental studies of crayfish
- Butterfly emergence and growth
- Bobwhite quail reproduction
- Surface water monitoring with sediment testing
- Prospective groundwater study

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended use

Dow AgroSciences has applied for registration of Intrepid 240F Insecticide, a commercial end-use product containing the new active ingredient methoxyfenozide. Intrepid 240F Insecticide is for control of codling moth, Oriental fruit moth, the overwintering generation of oblique-banded and three-lined leafrollers, and the first generation of

western tentiform and spotted tentiform leafminers on apple. This product will provide suppression of winter moth, and the summer generation of oblique-banded and three-lined leafrollers on apple.

Application rates are as follows:

- 1.0 L product/ha for codling moth and Oriental fruit moth;
- 0.75 L product/ha for leafrollers and wintermoth; and
- 0.5 L product/ha for leafminers (first generation only).

Application timing depends on the pest, and is either during egg laying or near first egg hatch, or is timed to target young larvae. The minimum interval between applications is 10–14 days, if a second application is required. The maximum amount of product that can applied is 2 L product/ha/year (480 g a.i./ha/year). Application is by ground only.

7.1.2 Mode of action

The active ingredient of Intrepid 240F, methoxyfenozide, belongs to the diacylhydrazine class of insecticides. This compound mimics the activity of the insect moulting hormone (ecdysone) of larval Lepidoptera. After ingestion by a larva, methoxyfenozide binds to the ecdysone receptor sites and the larva is stimulated to moult. Since the insect is not able to metabolize methoxyfenozide, the compound remains attached to the receptor site, resulting in an incomplete and lethal moult. The larva stops feeding after ingestion of methoxyfenozide, and eventually dies.

7.1.3 Crops

Intrepid 240 F Insecticide is for use on apples.

7.1.4 Effectiveness against pest

7.1.4.1 Codling moth on apple

Application rate for control of codling moth is 1.0 L product/ha (240 g a.i./ha). For control of first generation codling moth, Intrepid 240 F Insecticide is applied before first egg hatch (80–110 degree days Celsius) after BIOFIX, with a lower threshold of 10°C and an upper threshold of 31°C). Biofix is set when the first consistent moth catch has been made in pheromone-baited traps within the orchard. Re-application is recommended 10–14 days later if monitoring indicates this is required. For control of the second generation of codling moth, timing is based on first egg hatch after a new Biofix is established. If a second application is required, it would be applied 10–14 days later.

Six efficacy trials were submitted from western North America (four from Washington and two from British Columbia), and seven studies were submitted from eastern North America (four from Ontario, two from Nova Scotia, and one from West Virginia) to support the proposed label claims for codling moth. In western North America,

application rates tested ranged from 168–336 g a.i./ha, and in eastern North America, tested application rates ranged from 120–240 g a.i./ha. However, the same application rates were not tested in all trials, and only nine trials tested two different rates in the same trial.

Application methods were airblast sprayer or truck-mounted handgun. In almost all trials, spray volumes were approximately 1000 L/ha applied by airblast sprayer (dilute or concentrate spray not specified) or 3000 L/ha applied by a truck-mounted handgun as a dilute spray. One trial specifically tested a concentrate spray, 600 L/ha, applied by airblast sprayer. The number of applications ranged from one to four, and assessments of percent fruit damage were made at the end of the first generation, at the end of the second generation or at harvest. Assessments were not made after each application, and in some cases were made only after four applications. Azinphos-methyl was the most commonly used commercial standard. Pest pressure ranged from low to moderately high.

Data from Washington demonstrated that mean percent reduction in fruit damage provided by an application rate of 168 g a.i./ha (ranging from 20–63%) was numerically lower than that obtained with 337 g a.i./ha (ranging from 66–91%). Other application rates were not tested in Washington, but the data indicated that the lowest effective application rate was higher than 168 g a.i./ha.

Both trials from British Columbia tested application rates of 240 and 336 g a.i./ha, and results were assessed at harvest after four applications. There was no significant difference in mean percent fruit damage between the two application rates. Mean percent reduction in fruit damage was identical for both rates in the first trial (86–88%), but was numerically better for the higher rate in the second trial. However, results from the second trial were based on small plots (two-tree plots), a small number of replicates (four), low pest pressure and applications that may not have been timed correctly; these data are not sufficient evidence to support the higher application rate for control of codling moth.

Results from two trials in eastern North America that made side-by-side comparisons of 180 and 240 g a.i./ha demonstrated that the lower rate provided 64–78% reduction in fruit damage, while the higher rate provided 73–83% reduction. Other studies in eastern North America that tested 240 g a.i./ha also showed mean percent reduction in fruit damage ranged from 74–93%.

In all trials, performance of methoxyfenozide at a rate of 240 g a.i./ha was comparable to that of the commercial standard (azinphos-methyl in most trials).

In conclusion, an application rate of 240 g a.i./ha for control of codling moth was supported by efficacy trials, which indicated that this rate was close to the lowest effective rate. Results with lower rates appeared to be less consistent. However, mean reductions in percent fruit damage were variable for all rates tested, and was probably

influenced by factors such as application timing, spray volume and coverage. As factors such as timing and coverage are essential for consistent performance, it is critical that use directions on the label are followed.

7.1.4.2 Oriental fruit moth on apple

Five studies were submitted (four from the mid-Atlantic United States and one from Ontario); two of these studies were not acceptable because other insecticides that could have affected the results were applied during the trials. Because codling moth was also present in the study sites, larvae found internally in samples of damaged fruit were identified to estimate the ratio of codling moth to Oriental fruit moth (OFM) present in damaged apples during assessment. One trial also included the lesser apple worm (*Grapholita prunivora*) in internal larval assessments, although the population was very low.

Application rates tested were 157–360 g a.i./ha. Mean percent reduction in fruit damage ranged from 66–87% for these application rates, and from 73–87% for an application rate of 240 g a.i./ha. A lowest effective rate for control of OFM on apple was not established. Applications of methoxyfenozide were timed for control of codling moth, not for control of the OFM. However, growers will likely manage these two pests on apple in the same way, and time applications for control of the codling moth.

In conclusion, the application rate of 240 g a.i./ha, which is supported for control of codling moth on apple, is acceptable for the OFM on apple. Growers are likely to manage these two pests on apple together, and applications are likely to be timed for codling moth. This timing will not be optimal for Oriental fruit moth in all cases, but will likely be close.

7.1.4.3 Leafrollers on apple (oblique-banded and three lined leafrollers); overwintering generation

Three trials conducted in Ontario from 1999–2001 were provided for the oblique-banded leafroller (OBLR), and three trials conducted in Washington in 1999 and 2000 were provided for *Pandemis pyrusana*. Results for *Pandemis pyrusana* can be extrapolated to *Pandemis limitata*, the three-lined leafroller, which is the present in Canada (mainly in British Columbia). When both species (OBLR and the three-lined leafroller) are present in an orchard, growers will manage them in the same way.

For the OBLR, one application of methoxyfenozide was applied at petal fall, and rates tested were 84, 90, 180 and 240 g a.i./ha, with a dilute spray volume of 3000 L/ha, applied with a truck-mounted handgun sprayer. No more than two application rates were tested in the same trial. Performance of methoxyfenozide was the same or better than the commercial standard, tebufenozide. Performance was assessed by percent terminal infestation. Results showed that the lowest effective rate for methoxyfenozide was probably higher than 84–90 g a.i./ha. Application rates of 180 and 240 g a.i./ha were

directly compared in only one trial; in this trial, performance of the two rates was not significantly different: ≥ 86% reduction of terminal infestation in both cases.

Two of the three trials targeting the overwintering generation of *Pandemis* leafrollers provided limited information because an untreated control was not included. In the third trial, one application of methoxyfenozide was applied against the overwintering generation in early May. Application rates tested were 100, 134, 220 and 280 g a.i./ha. When the number of dead larvae per 15 terminals was assessed, all treatments had significantly more dead larvae than the untreated control, but results were not statistically different for the lowest and highest rate, and were similar for the two intermediate rates.

In conclusion, one application at a rate of 180 g a.i./ha can be supported for control of the overwintering generation of leafrollers (oblique-banded and three-lined leafrollers). Performance was numerically better, but not always statistically better, than the commercial standard, tebufenozide.

7.1.4.4 Leafrollers on apple (oblique-banded and three lined leafrollers); summer generation

Ten studies (eight studies on OBLR [six from Ontario and two from New York] and two studies on *Pandemis pyrusana* from Washington) conducted between 1998–2000 were submitted to support proposed label claims for the summer generation of leafrollers. Application rates tested were 120–360 g a.i./ha. Assessment methods included measurement of percent infestation of terminals, and assessment of fruit damage (which also included damage from the overwintered generation). Number of applications against the summer generation of leafrollers ranged from one to three. Application was by airblast sprayer (spray volume of 1000 L water/ha) or truck-mounted handgun (dilute spray with a spray volume of 3000 L water/ha).

The performance of methoxyfenozide for the application rates tested was inconsistent between trial, application rate and parameter assessed, and a consistent rate effect was not established. Compared to untreated plots, mean percent reduction in the assessed parameters ranged from 44 to100%. This can in part be explained by the extended emergence period of the summer generation of these leafroller species, which makes optimum application timing difficult. The performance of methoxyfenozide was not significantly different from, or was better than the commercial standard, which was tebufenozide in most trials.

In conclusion, an application rate of 180 g a.i./ha can be supported for suppression of the summer generation of leafrollers. This is the same application rate supported for the overwintered generation.

7.1.4.5 Winter moth on apple

Two studies conducted during 1998 and 1999 in Nova Scotia were submitted to support proposed label claims for winter moth. One application of methoxyfenozide was made in early May and assessment of fruit damage was made at harvest, which was over 80 days after treatment. One study also provided percent mortality of winter moth larvae per fruit cluster four days after treatment. However, pretreatment larval counts were not provided, so the percent mortality data did not provide meaningful information.

Application rates tested were 240 and 360 g a.i./ha. Application was by a mist sprayer delivering a concentrate spray with a water volume of 600 L/ha. Evaluation of fruit damage at harvest did not demonstrate a rate effect, and mean percent reduction in fruit damage ranged from 24 to 50%. Lowest effective rate was not established. Performance of the commercial standard (tebufenozide) was not significantly different or was better than that of methoxyfenozide. However, fruit damage assessments made over 80 days after application may be misleading, and a valid assessment of larval populations 7–14 days after treatment may have demonstrated better performance for methoxyfenozide.

In conclusion, an application of methoxyfenozide at petal fall directed against winter moth larvae can reduce fruit damage caused by winter moth. However, a lowest effective rate was not established. Extrapolation from the rate accepted for leafrollers, 180 g a.i./ha, is used to establish an acceptable application rate for suppression of winter moth.

7.1.4.6 Leafminer on apple (spotted tentiform leafminer and western tentiform leafminer)

Eleven efficacy trials conducted on leafminer between 1992 and 2000 were provided (eight studies on spotted tentiform leafminer [six from Ontario and two from Pennsylvania] and three studies on tentiform leafminer from Washington). Results from spotted tentiform leafminer can be extrapolated to western tentiform leafminer because of their similar life cycles and the similar feeding damage to apple trees. Application rates tested ranged from 67 to 336 g a.i./ha, and spray volumes were approximately 500–1000 L/ha (applied by airblast sprayer), or 3000 L/ha (applied by truck-mounted handgun sprayer as a dilute spray). Assumptions about whether application by airblast sprayer was as a dilute or concentrated spray were based on tree size. In three studies, applications were timed for other pests (e.g., codling moth, leafrollers) and not for leafminer. The different spray volumes used and application timings for other insect pests made interpretation of results for some studies difficult.

In the nine studies in which application timing was specifically for leafminer, eight studies targeted the first generation of leafminers, and one targeted the second generation. These studies examined the efficacy of applications that targeted different developmental stages of leafminers (e.g., egg hatch or sapfeeder stage). In these studies, number of applications per generation of leafminers was one or two. Assessment was based on the number of larvae or the number of mines per cluster or terminal.

Studies on the first generation of leafminers that tested multiple application rates in the same trial did not demonstrate a benefit to using rates higher than 120 g a.i./ha. when applications were timed correctly. Timing of application appeared to be critical, and optimal timing for the first generation was during egg hatch, so that young larvae were targeted. Trials that tested more than one application rate indicated that 120 g a.i./ha was close to the lowest effective application rate, with mean reduction in number of mines ranging from 83 to 94%. Performance was as good as or better than the commercial standard, tebufenozide.

In conclusion, efficacy data supported an application rate of 120 g a.i./ha against the first generation of tentiform leafminers (spotted tentiform leafminer and western tentiform leafminer). Results demonstrated that application timing is critical, and methoxyfenozide should be applied during egg hatch to target very young larvae. Data on the second generation were not sufficient to evaluate efficacy. Later generations tend to have a more prolonged hatching period, and timing may be more difficult to achieve for adequate control.

7.1.5 Total spray volume

The active ingredient, methoxyfenozide, belongs to the diacylhydrazine class of insecticides, and Intrepid 240 F Insecticide is effective mainly after ingestion by larvae. Therefore, thorough uniform coverage of all foliage and fruit is essential for good control. The minimum recommended spray volume is 1000 L water/ha. If adequate spray coverage of plant canopy requires less solution per hectare, spray volume must be adjusted accordingly, while using the same spray concentration (ratio of litres of product to litres of water). The application rates (litres of product/ha) listed for each pest on the label for Intrepid 240 F Insecticide cannot be exceeded.

7.2 Phytotoxicity to target plants (including different cultivars) or to target plant products (OECD 7.4)

No phytoxicity was observed when the proposed end-use product was applied alone. Adverse effects were occasionally observed when the proposed end-use product was tank-mixed with adjuvants or spreaders/stickers. However, the applicant did not propose that using adjuvants or spreader/stickers is needed to increase efficacy of the proposed end-use product.

7.3 Observations on undesirable or unintended side effects (OECD 7.5)

Examples of unintended side effects include those on beneficial and other non-target organisms, on succeeding crops, other plants or parts of treated plants used for propagating purposes (e.g., seed, cutting, runners).

Data or observations on toxicity to non-target organisms (e.g., beneficial insects such as parasitoids and predators) were not reported in efficacy trials.

7.3.1 Impact on succeeding crops (OECD 7.5.1)

Undesirable or unintended side effects on succeeding crops were not reported and are not expected.

7.3.2 Impact on adjacent crops (OECD 7.5.2)

Undesirable or unintended side effects on adjacent crops were not reported and are not expected.

7.3.3 Impact on seed viability (OECD 7.5.3)

Not applicable.

7.4 Economics

No data on the projected economic value of using Intrepid 240 F Insecticide to the apple industry in Canada were provided by the applicant. Approximately 25 825 ha were planted for commercial apple production in Canada in 2001, with the largest percentage in Ontario (38%), followed by Quebec (26%), British Columbia (23%) and Nova Scotia (10%). The proposed end-use product has potential for use in all apple-growing areas of Canada, for both a primary pest (i.e., codling moth) and secondary pests (e.g., leafrollers and tentiform leafminers).

7.5 Sustainability

7.5.1 Survey of alternatives

The major insecticide active ingredients currently registered for control of the proposed pests on apple include, but are not necessarily limited to, the following:

Pest	Available alternative active ingredients
Codling moth	carbamates (carbaryl, methomyl); organophosphates (azinphos-methyl, diazinon, dichlorvos, dimethoate, malathion, phosalone, phosmet); organochlorines (endosulfan); pyrethroids (cyhalothrin-lamda, cypermethrin, deltamethrin, permethrin); neonicotinoids (acetamiprid); tebufenozide; and pheromone-based mating disruption

Pest	Available alternative active ingredients
Leafrollers (oblique-banded, leafroller, three-lined leafroller)	organophosphates (azinphos-methyl, diazinon, methidathion, parathion, phosalone, phosmet); carbamates (carbaryl); pyrethroids (lambda-cyhalothrin); tebufenozide; *Bacillus thuringiensis*; spinosad; and pheromone-based mating disruption
Tentiform leafminer (spotted tentiform leafminer, western tentiform leafminer)	avermectin (abamectin); carbamates (carbaryl, methomyl, oxamyl); neonicotinoids (imidacloprid, acetamiprid); organophosphates (diazinon, phosmet); pyrethroids (permethrin, cypermethrin, deltamethrin, cyhalothrin-lambda); and tebufenozide
Winter moth	pyrethroids (permethrin, deltamethrin); organophosphates (azinphos-methyl); tebufenozide; *Bacillus thuringiensis*
Oriental fruit moth	pheromone-based mating disruption

7.5.1.1 Non-chemical control practices

Non-chemical methods for controlling codling moth include sterile male release (currently in use in British Columbia), predation by ground beetles (carabids), ants and crickets as well as parasitization by wasps. Removal of nearby sources of infestation such as abandoned orchards or wild volunteer trees can reduce levels of codling moth infestation. Routine hygiene, such as removal of infested fruit as well as removal of boxes and bins that can provide pupation sites, is an important component of cultural control. Placing bands (e.g., corrugated cardboard bands) on the trunks or branches of trees to intercept larvae seeking sites for pupation, and later removing and destroying the bands, will help reduce populations when combined with other control strategies.

Natural enemies, particularly parasitoids, have an effect on the population dynamics of winter moth, tentiform leafminers and leafrollers.

7.5.1.2 Chemical control practices

See Section 7.5.1.

7.5.2 Compatibility with current management practices, including integrated pest management

Intrepid 240F Insecticide is compatible with current management practices, including integrated pest management (IPM). The proposed end-use product can be applied with conventional ground application equipment (e.g., airblast sprayer). Growers are familiar with the proposed use instructions to determine application timing (e.g., the use of pheromone-baited traps to monitor adult moth populations), and with monitoring techniques to determine if and when applications are needed.

7.5.3 Contribution to risk reduction

Intrepid 240 F Insecticide is potentially an alternative to older classes of insecticides (e.g., organophosphates) listed in Section 7.5.1 for use against the proposed pests on apple. Methoxyfenozide is in the same group of insecticides (see Section 7.5.4) as tebufenozide, which is registered for use on apple against several of the proposed pests.

Methoxyfenozide and tebufenozide represent an alternative class of insecticides for pest management in apple orchards. However, potential cross-resistance between this group of insecticides (group 18) and other groups of insecticides used for control of the proposed pests (e.g., azinphos-methyl for codling moth control; see Section 7.5.4) should be monitored.

7.5.4 Information on the occurrence or possible occurrence of the development of resistance

Methoxyfenozide is a diacylhydrazine insecticide, which is a second generation ecdysone agonist. Tebufenozide, which is in the same class of compounds, has been registered in Canada since 1996 for use on apples for many of the same pests for which methoxyfenozide is proposed. Diacylhydrazines selectively bind to the functional ecdysone receptor in Lepidopteran larvae.

According to PMRA Regulatory Directive DIR99-06, *Voluntary Resistance-Management Labelling Based on Target Site/Mode of Action*, methoxyfenozide and tebufenozide are group 18 insecticides. Resistance management statements have been incorporated into the proposed label for Intrepid 240 F Insecticide as outlined in DIR99-06.

Development of resistance to methoxyfenozide has not been reported, but studies have indicated that it is possible (Smirle et al. 2002). Bioassays examining resistance and cross-resistance to different insecticides in populations of leafrollers (*Choristoneura rosaceana* and *Pandemis pyrusana*) in British Columbia (Smirle et al. 2002) have also demonstrated the potential for development of cross-resistance between azinphos-methyl and diacylhyradazine insecticides, including methoxyfenozide. Similar results have been obtained for populations of codling moth in the Pacific northwest (Knight 2004). These

studies suggest that a resistance-management strategy for the proposed pests involving rotation of these materials should be monitored.

7.6 Conclusions

The following conclusions are based on a complete review of the submitted efficacy data for Intrepid 240 F Insecticide:

- Adequate efficacy data have been submitted to support controlling the following pests on apple: codling moth, Oriental fruit moth, overwintering generation of leafrollers (oblique-banded leafroller and three-line leafroller), and the first generation of leafminers (spotted tentiform leafminer and western tentiform leafminer). Adequate efficacy data have been provided to support suppression of winter moth and the summer generation of leafrollers (oblique-banded leafroller and three-line leafroller) on apple. Application rates that are supported by efficacy data vary for each pest; these are listed Table 7.6.1.

- Application timing and adequate coverage are important for consistent performance of Intrepid 240 F Insecticide. Application timing is summarized in Table 7.6.1, and varies depending on the target pest.

- The maximum amount of Intrepid 240 F Insecticide that can be applied is 2 L product/ha/year (480 g a.i./ha/year). The minimum interval between applications is 10–14 days, if required. Therefore, growers will use Intrepid 240 F Insecticide as part of an IPM program.

- No phytotoxic effects to foliage or fruit were reported in provided efficacy trials when Intrepid 240 F Insecticide was applied alone.

Table 7.6.1 Acceptable pests and application rates for use of Intrepid 240 F Insecticide on apples

Pest	Application rate (L product/ha)	Application rate (g a.i./ha)	Summary of application timing
Note: Do not exceed 2 L product/ha/year (480 g a.i./ha/year)			
Codling moth	1	240	For the control of the first generation, apply before first egg hatch, as determined by BIOFIX using pheromone-baited traps. Monitor populations and re-apply 10–14 days later, if required.

Pest	Application rate (L product/ha)	Application rate (g a.i./ha)	Summary of application timing
Oriental fruit moth	1	240	Apply at first egg hatch of the targeted generation. Monitor populations and re-apply 10–14 days later, if required.
Oblique-banded leafroller, three-lined leafroller on apple (overwintering generation)	0.75	180	Apply during late bloom to early petal fall when larvae are actively feeding and before they roll up in leaf terminals.
Oblique-banded leafroller, three-lined leafroller (suppression of summer generation)	0.75	180	Apply at first egg hatch, as determined by BIOFIX using pheromone-baited traps. Re-apply 10–14 days later, if monitoring indicates this is needed.
Winter moth on apple (suppression)	0.75	180	Monitor apple buds for larvae of winter moth. Consult provincial guidelines for treatment thresholds and application timing.
Spotted tentiform leafminer, western tentiform leafminer (first generation only)	0.5	120	Apply at first egg hatch of the first generation.

7.6.1 Summary

Dow AgroSciences has applied for registration of Intrepid 240 F Insecticide, a commercial end-use product containing the new active ingredient methoxyfenozide. Adequate efficacy data have been submitted to support use of Intrepid 240 F Insecticide for control of codling moth, Oriental fruit moth, oblique-banded leafroller and three-lined leafroller (overwintering generation), spotted tentiform leafminer (first generation only) and western tentiform leafminer (first generation only) on apple. Efficacy data support the use of Intrepid 240 F Insecticides for suppression of winter moth and the summer generation of oblique-banded leafroller and three-lined leafroller on apple. Acceptable application rates and a summary of application timings are provided in Table 7.6.1. The

maximum amount of product that can be applied per year is 2 L product/ha/year (480 g a.i./ha/year). The minimum interval between applications is 10–14 days, if required.

No phytotoxic effects to foliage or fruit were reported in submitted efficacy trials when Intrepid 240 F Insecticide was applied alone.

The technical grade of active ingredient, methoxyfenozide, belongs to the diacylhydrazine class of insecticides. This class of compounds are second generation ecdysone agonists, and the mode of action is mainly by ingestion by Lepidopteran larvae. Therefore, application timing and thorough coverage are critical for consistent performance of this product.

8.0 Toxic Substances Management Policy considerations

During the review of Intrepid 240F Insecticide, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this product does not meet TSMP Track 1 criteria because it does not bioaccumulate in fish and mammals.

- Studies in fish have shown that the bioaccumulation factor (BAF) for methoxyfenozide (or the bioconcentration factor [BCF]) is 8.9, which is below the TSMP Track 1 cutoff criterion of BAF ≥ 5000 (or BCF ≥ 5000). The *n*-octanol–water partition coefficient (log K_{ow}) is 3.72, which is also below the TSMP Track 1 cutoff criterion of ≥ 5.0. Mammalian toxicology studies indicate that methoxyfenozide does not accumulate in tissues and is excreted in feces and urine.

- Although data on the persistence in air were not available, the vapour pressure (1.33×10^{-5} Pa) and Henry's Law constant (1.935×10^{-7} atm·m^3/mol) indicate that methoxyfenozide will not volatilize from water or moist soil under field conditions. The water DT_{50} for an anaerobic water–sediment system was 654 days, and the DT_{50} for an aerobic water–sediment system was 387–963 days. The DT_{50}s of methoxyfenozide in soil ranged from 239 to 433 d. These values are above the TSMP Track 1 cutoff criteria for persistence in sediment (≥ 365 d), soil (≥ 182 days) and water (≥ 182 d).

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1 The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics.

2 Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1 800 267-6315 within Canada or (613) 736-3799 outside Canada (long distance charges apply); Fax: (613) 736-3758; E-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca

- The toxicity of methoxyfenozide is described in sections 3.0 and 6.0.

- Methoxyfenozide formed one major transformation product, RH-117236, in a laboratory study of aerobic biotransformation in water. RH-117236 reached a maximum concentration of 12.62% by 91 DAT in clay soil, but is considered transient as it decreased to 8.63 by 120 DAT. RH-117236 does not meet TSMP criterion for persistence.

- Methoxyfenozide (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

- All formulants in Intrepid 240F are either on USEPA List 3 or List 4. The formulated product does not contain any formulants known to contain TSMP Track 1 substances.

Therefore, the use of Intrepid 240F Insecticide is not expected to result in the entry of TSMP Track 1 substances into the environment.

9.0 Proposed regulatory decision

Methoxyfenozide technical and the end-use product Intrepid 240F Insecticide have been granted temporary registration for use on apples, pursuant to Section 17 of the Pest Control Products Regulations, subject to the generation of the following studies:

- Terrestrial arthropods (predators, parasites and collembola)
- Honeybee brood
- Sediment toxicity test with *Hexagenia*
- Bioconcentration using saltwater bivalve molluscs
- Frog embryo teratogenesis
- Developmental studies of crayfish
- Butterfly emergence and growth
- Bobwhite quail reproduction
- Surface water monitoring study with sediment testing
- Prospective groundwater study

Should methoxyfenozide be expanded to large-scale agricultural use, an edge-of-field runoff study (and if needed, an aquatic field study) will be required.

For the apple residue trials although zonal representation was fulfilled, at the end of the approval process, the residue data reflected a Good Agricultural Practice (GAP) that was 3 fold larger. This was a consequence of addressing environmental concerns, which resulted in reducing the number of applications from four to two per year. Considering that this compound is an insect growth regulator with a mode of action that is specific to

its target, that the dietary risk profile of this compound indicated a large margin of safety, and that the seasonal rate approved is not related to the efficacy concerns, the PMRA concluded that additional residue data representative of the Canadian use pattern will not be required.

List of abbreviations

ACN	acetonitrile
ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
ARTF	Agricultural Re-entry Task Force
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
BWI	body weight per individual
bwg	body-weight gain
CAS	Chemical Abstracts Service
CEC	cation exchange capacity
cm	centimetre(s)
CMC	carboxymethylcellulose
d	day(s)
DACO	data code
DALA	days after last application
DAT	days after treatment
DCM	dichloromethane
DFR	dislodgeable foliar residue
DI	daily intake
DMP	dimethylphenyl ring
DT_{50}	dissipation time 50%
dw	dry weight
EC	electron capture
EC_{50}	effects concentration 50%
ECD	Electron Capture Detector
EEC	expected environmental concentration
EP	end-use product
EXAMS	Exposure Analysis Modeling System
FC	food consumption
FLC	flowable concentrate
fw	fresh weight
g	gram
GC	gas chromatography
GGT	gamma-glutamyl transferase
GLC	gas-liquid chromatography
h	hour
ha	hectare
HAFT	highest average field trial
Hb	hemoglobin
Hct	hematocrit
HCl	hydrochloric acid
HDPE	high density polyethylene

HPLC	high performance liquid chromatography
ILV	independent laboratory validation
ind	individual
IUPAC	International Union of Pure and Applied Chemistry
K_1	uptake rate constant
K_2	depuration rate constant
K_{ow}	*n*-octanol–water partition coefficient
K_d	adsorption quotient
K_{oc}	adsorption quotient normalized to organic carbon
kg	kilogram
L	litre
LC	liquid chromatography
LC-UV	liquid chromatography with ultraviolet detection
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LEACHM	Leaching Estimation and Chemistry Model
LOEC	lowest observed effect concentration
LOD	level of detection
LOQ	level of quantitation
LSC	liquid scintillation counter
M	mole
m	metre
MAS	maximum average score
MCH	mean corpuscular hemaglobin
mCi	millicurrie
MCV	mean corpuscular volume
mg	milligram
MIS	maximum irritation score
mL	millilitre
M/L/A	mixer/loader/applicator
MMAD	mass median aerodynamic diameter
mm Hg	millimetre of mercury
MOP	methoxyphenyl ring
MRL	maximum residue limit
MS	mass spectrometry
MSPD	matrix solid phase dispersion
NAC	N-acetyl cysteine
ng	nanogram
nm	nanometre
NOEC	no observed effect concentration
NP	nitrogen phosphorus
OBLR	oblique-banded leafroller
OECD	Organisation for Economic Cooperation and Development
OFM	Oriental fruit moth
OM	organic matter
NOAEL	no observed adverse effect level

NOEC	no observed effect concentration
NOEL	no observed effect level
PAM	Pesticide Analytical Manual
PBI	plantback interval
PCP	pest control product
PES	post-extraction solids
PHED	pesticide handlers exposure database
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
PRZM	Pesticide Root Zone Model
Q*	cancer risk factor
RPLC-UV	reversed phase liquid chromatography with ultraviolet detection
ppm	parts per million
RAC	raw agricultural commodity
RBC	red blood cell
ROC	residue of concern
RQ	risk quotient
RSD	relative standard deviation
SD	standard deviation
SPE	solid phase extraction
T_{90}	90% clearance time
TB	t-butyl moiety
TGAI	technical grade active ingredient
TLC	thin layer chromatography
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
µg	micrograms
USEPA	United States Environmental Protection Agency
UV	ultraviolet
vol	volume
v:v	volume per volume
w:v	weight per volume

Appendix I Toxicology

Note: Effects on associated blood and non-blood parameters reported in the table that are at or below the NOAEL were considered treatment-related but not adverse.

Unless specified, effects reported apply for both sexes.

METABOLISM

Rate and extent of absorption: Following oral administration (10 mg/kg bw), the absorption of methoxyfenozide was 70 and 62% of the administered dose (AD) in males and females respectively. The absorption was not determined at the high dose (1000 mg/kg bw). The absorption of methoxyfenozide was very rapid as peak plasma levels (C_{max}) were observed 15–30 minutes post-dosing with the low or high dose.

Excretion: The primary route of excretion is via the feces; 81–93% of the AD was excreted in feces and 4–12% of the AD was excreted in urine within 48 hrs following dosing with the low or high dose. Urinary excretion was about 2× greater in females relative to males. Seventy-two hrs following administration, 64 and 38% of the AD were excreted in the bile of males and females respectively treated at the low dose. These results suggest gender differences with regard to hepatic and/or renal handling/metabolism of methoxyfenozide.

Distribution/target organs: At C_{max}, the highest percentage of the AD was found in the liver; 4.2–9.3% and 1.47–4.58% of the AD in low-dose and high-dose animals respectively. Five days following single dose administration (10 or 1000 mg/kg bw) tissue levels of ^{14}C were undetectable or very low. The liver was the tissue with the highest ^{14}C concentration; 0.07–0.11% of AD in males and 0.01–0.02% of AD in females. Tissue and the residual carcass contained only 0.07–0.23% of the AD.

Metabolism/toxicologically significant compounds: ^{14}C-methoxyfenozide is extensively metabolized; including the parent compound, 34 metabolites, of which 28 were identified, were isolated from pooled fecal and urine samples. Eight metabolites, including the parent compound, were found present at greater than or equal to 5% of the AD and accounted for 74–90% of the AD. The majority of metabolites were recovered in feces. The primary metabolic pathway involves demethylation of the A-ring methoxy moiety to form the corresponding phenol (metabolite M-B) which is in turn conjugated to glucuronic acid (metabolite M-L). The hydroxylation of the B-ring methyl moiety is also an important pathway. The metabolite M-B accounted for 11–25 and 27–34% of the AD for low-dose females and males respectively, and for 15–18 and 18–25% of the AD for the high-dose males and females respectively. The metabolite M-F, B-ring-hydroxylated—B metabolite, comprised 14–24% of the AD for all groups and metabolites M-D, M-H, M-I, and M-L each comprised 5–12% of the AD.

Twenty-four metabolites were found and characterized in the bile. M-L (13–18% of AD) and M-Q_1 (5–11% of AD; A-ring glucuronide of metabolite M-F) were the primary metabolites found in bile samples. M-S was present at 2% of the AD in both sexes. M-AH (unidentified) was present at 4 and 1% of the AD in males and females respectively. These metabolites accounted for 65% (males) and 83% (females) of the bile (0–6 hr) radioactivity.

Pretreatment of animals for two-weeks in the diet (200 ppm) or for 5 days (^{14}C-methoxyfenozide; 10 mg/kg bw, po) did not substantially change the ^{14}C absorption or distribution profile. The repeated administration also provided no evidence of bioaccumulation.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
ACUTE STUDIES – END-USE PRODUCT (Intrepid 240F Insecticide)			
Oral	Rat/Crl:CD BR (6/sex) 5000 mg/kg bw (limit dose)	LD_{50} > 5000 mg/kg bw	**Low oral toxicity** No treatment-related clinical signs of toxicity observed.
	Mouse/Crl:CD-1 (ICR) BR (6/sex) 5000 mg/kg bw (limit dose)	LD_{50} > 5000 mg/kg bw	**Low oral toxicity** No treatment-related clinical signs of toxicity observed.
Dermal	Rat/Crl:CD BR (6/sex) 2000 mg/kg bw (limit dose)	LD_{50} > 2000 mg/kg bw	**Low dermal toxicity** No treatment-related clinical signs of toxicity observed.
Inhalation	Rat/Crl:CD BR (6/sex) 0.9 mg/L (max attainable conc.)	LC_{50} > 0.9 mg/L	**Inhalation toxicity considered low** Based on the low volatility of the active ingredient and the generation of large particles during application (MMAD ≥ 150 μm) No treatment-related clinical signs of toxicity observed.
Primary eye irritation	Rabbit/New Zealand White (6 male)	MIS = 0 at 1 hr MAS = 0 for 24, 48 and 72 hrs	**Non-irritating to the eyes**
Primary dermal irritation	Rabbit/New Zealand White (6 male)	MIS = 0 at 1 hr MAS = 0 for 24, 48 and 72 hrs	**Non-irritating to skin**
Dermal sensitization (maximization test)	Guinea Pig/Hartley (20 animals test group)	Negative	**Not a sensitizer**
ACUTE STUDIES – TECHNICAL			
Oral	Rat/Crl: CD BR (6/sex) 5000 mg/kg bw (limit dose) in 0.5% methylcellulose	LD_{50} > 5000 mg/kg bw	**Low oral toxicity** No treatment-related clinical signs of toxicity observed.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
	Mouse/Crl: CD-1 (ICR) BR (6/sex) 5000 mg/kg bw (limit dose) in 0.5% methyl cellulose	LD_{50} > 5000 mg/kg bw	**Low oral toxicity** No treatment-related clinical signs of toxicity observed.
Dermal	Rat/Crl:CD BR (6/sex) 5000 mg/kg bw (limit dose)	LD_{50} > 5000 mg/kg bw	**Low dermal toxicity** No treatment-related clinical signs of toxicity observed.
Inhalation	Rat/Crl:CD BR (6/sex) 4.3 mg/L (limit concentration)	LC_{50} > 4.3 mg/L	**Low inhalation toxicity** No treatment-related clinical signs of toxicity observed.
Primary eye irritation	Rabbit/New Zealand White (6 male)	MIS = 9.0 at 1 hr MAS = 0 for 24, 48 and 72 hrs	**Minimally irritating to the eyes**
Primary dermal irritation	Rabbit/New Zealand White (6 male)	MIS = 0 at 1 hr MAS = 0 for 24, 48 and 72 hrs	**Non-irritating to skin**
Dermal sensitization (maximization test)	Guinea Pig/Hartley (20 animal test group)	Negative	**Not a sensitizer**
ACUTE STUDIES – METABOLITE			
Oral **Methoxyfenozide metabolite: RH-117236 (M-B)**	Mouse/Crl: CD-1 (ICR) BR (6/sex) 5000 mg/kg bw (limit dose) in 0.5% methylcellulose.	LD_{50} > 5000 mg/kg bw	**Low oral toxicity** No treatment-related clinical signs of toxicity observed.
SHORT TERM			
28-day dermal	Rat/Crl: CD BR (10/sex/dose) 0, 75, 300 or 1000 mg/kg bw/day	NOAEL: 1000 mg/kg bw/day (♂ and ♀) LOAEL: > 1000 mg/kg bw/day	**No adverse effects observed**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
4-week dietary and 4-week recovery period (blood recovery study)	Dog/Beagle (4 males/dose) 0 or 30 000 ppm equal to: 0 or 1036 mg/kg bw/day	N/A	**After 4 weeks of treatment:** No mortality, no effects on BW, no clinical signs of toxicity. - ↑ methemoglobin, MCV, MCH and platelets and ↓ RBC, hemoglobin, and hematocrit. **After 4-week recovery period:** Complete recovery and reversibility of hematological effects.
90-day dietary	Rat/Crl: CD BR (10/sex/dose) 0, 50, 250, 1000, 5000 or 20 000 ppm equal to: ♂: 0, 3.4, 17.0, 69, 353 or 1369 mg/kg bw/day ♀: 0, 3.7, 19.1, 72, 379 or 1531 mg/kg bw/day	NOAEL: ♂: 1369 mg/kg bw/day ♀: 1531 mg/kg bw/day LOAEL: ♂: > 1369mg/kg bw/day ♀: > 1531 mg/kg bw/day	**No adverse effects observed** ≥ 353/379 mg/kg bw/day: ↑ liver periportal hepatocellular hypertrophy; ↑ liver weight (males) 1369/1531 mg/kg bw/day: ↑ liver weight. - ↓ RBC, hemoglobin and hematocrit (females)
90-day dietary	Mouse/Crl: CD-1 (10/sex/dose) 0, 70, 700, 2500 or 7000 ppm equal to: ♂: 0, 11.9, 113, 428 or 1149 mg/kg bw/day ♀: 0, 17.4, 165, 589 or 1742 mg/kg bw/day	NOAEL: ♂: 1149 mg/kg bw/day ♀: 1742 mg/kg bw/day LOAEL: ♂: > 1149 mg/kg bw/day ♀: > 1742 mg/kg bw/day	**No adverse effects observed**
90-day dietary * Treatment groups were sacrificed at 13 weeks except for the low-dose group. The low-dose group was treated for 15 weeks with 15 ppm followed by 15 000 ppm for an additional 6 weeks	Dog/Beagle (4/sex/dose) 0, 15*, 50, 500 or 5000 ppm equal to: ♂: 0, 0.6 (*422), 2.0, 21 or 198 mg/kg bw/day ♀: 0, 0.6 (*460), 1.9, 20 or 209 mg/kg bw/day	NOAEL: ♂: 198 mg/kg bw/day ♀: 209 mg/kg bw/day LOAEL: ♂: > 198 mg/kg bw/day ♀: > 209 mg/kg bw/day	**No adverse effects observed**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
12-month dietary	Dog/Beagle (4/sex/dose) 0, 60, 300, 3000 or 30 000 ppm equal to: ♂: 0, 2.2, 9.8, 106 or 1152 mg/kg bw/day ♀: 0, 2.2, 12.6, 111 or 1199 mg/kg bw/day	NOAEL: ♂: 9.8 mg/kg bw/day ♀: 12.6 mg/kg bw/day LOAEL: ♂: 106 mg/kg bw/day ♀: 111 mg/kg bw/day	**≥ 106/111 mg/kg bw/day:** - ↑ platelets (males); ↑ methemoglobin; ↓ RBC, Hb, Hct and ↑ MCV, ↑bilirubin (females) **1152/1199 mg/kg bw/day:** - ↑platelets, ↑ MCH (females) - ↑bilirubin (males) - ↑ in nucleated RBC - ↑ liver and thyroid weights (males) - brown pigments consistent with hemosiderin in liver and spleen - bone marrow changes (↑ cellularity, hematopoietic cells, primary and precursor erythrocytes, ↓ fat vacuoles) - ↓ in bw (males)
CHRONIC TOXICITY/ONCOGENICITY			
18-months dietary	Mouse/Crl: CD-1 (60/sex/dose) 0, 70, 2800, or 7000 ppm equal to: ♂: 0, 10, 405 or 1020 mg/kg bw/day ♀: 0, 12.8, 529 or 1354 mg/kg bw/day	NOAEL: ♂: 1020 mg/kg bw/day ♀: 1354 mg/kg bw/day LOAEL: ♂: > 1020 mg/kg bw/day ♀: > 1354 mg/kg bw/day	**No adverse effects observed** No increase in tumour incidences observed.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
2-year dietary	Rat/Crl: CD BR (60/sex/dose 2 year or 10/sex/dose for 1 year) 0, 200, 8000 or 20 000 ppm equal to: ♂: 0, 10.2, 411 or 1045 mg/kg bw/day ♀: 0, 11.9, 491 or 1248 mg/kg bw/day	NOAEL: ♂: 10.2 mg/kg bw/day ♀: 11.9 mg/kg bw/day LOAEL: ♂: 411 mg/kg bw/day ♀: 491 mg/kg bw/day	**≥ 411/491 mg/kg bw:** - ↓ RBC, hemoglobin and hematocrit - ↑liver periportal hepatocellular hypertrophy and serum GGT. - ↑ liver weight, thyroid hypertrophy and altered thyroid colloid (↓ basophilia, irregular density or granulometry) in males. **1045/1248 mg/kg bw/day:** -↑ mortality in males (at latter stage of study) -↑ methemoglobin , ↑ liver weight, thyroid hypertrophy, altered thyroid colloid (↓basophilia, irregular density or granulometry) and severe chronic progressive glomerulonephropathy - In females: ↓ bw, ↑ adrenal weight, kidney pelvis epithelial cell hyperplasia, tissue mineralization (heart, aorta, kidney, stomach), fibrous osteodystrophy (femur, sternum), tissue inflammation (fore and glandular stomach) and erosion/ulceration of forestomach. No increase in tumour incidences observed.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
REPRODUCTION/DEVELOPMENTAL TOXICITY			
Multigeneration reproduction	Rat/Crl: CD BR (30/sex/dose) 0, 200, 2000 or 20 000 ppm in diet equal to: P parental animals: ♂: 0, 15, 153 or 1552 mg/kg bw/day ♀: 0, 18, 180 or 1821 mg/kg bw/day F_1 parental animals: ♂: 0, 19.1, 193 or 1956 mg/kg bw/day ♀: 0, 20.4, 203 or 2037 mg/kg bw/day	Parental systemic NOAEL: ♂: 153 mg/kg bw/day ♀: 181 mg/kg bw/day Parental systemic LOAEL: ♂:1552 mg/kg bw/day ♀: 1821 mg/kg bw/day Reproductive NOAEL: ♂:1552 mg/kg bw/day ♀: 1821 mg/kg bw/day Reproductive LOAEL: ♂: > 1552 mg/kg bw/day ♀: > 1821 mg/kg bw/day Offspring NOAEL: 1821 mg/kg bw Offspring LOAEL: > 1821 mg/kg bw	**Parental systemic effects (1552/1821 mg/kg bw/day):** -↑ liver weights, ↑ periportal, midzonal hepatocellular hypertrophy in P and F_1. - Minimal pigments (consistent with hemosiderin) in Kupffer cells in P (females) - ↓ bw (7%) and bwg (10%) in P males at end of treatment **Offspring effects:** No adverse effects observed **Reproductive effects:** No adverse effects observed
Teratogenicity	Rat/Crl:CD BR (25/dose) 0, 100, 300 or 1000 mg/kg bw/day in 0.5% aqueous sodium CMC; gavage dose from GD 5 to 15.	Maternal and developmental NOAEL: 1000 mg/kg bw/day (limit dose) Maternal and developmental LOAEL: > 1000 mg/kg bw/day	**No adverse effects observed**
Teratogenicity	Rabbit/New Zealand White (16/dose) 0, 100, 300 or 1000 mg/kg bw/day in 0.5% aqueous sodium CMC; gavage dose from GD 7 to 19	Maternal and developmental NOAEL: 1000 mg/kg bw/day (limit dose) Maternal and developmental LOAEL: > 1000 mg/kg bw/day	**No adverse effects observed**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
GENOTOXICITY			
Salmonella/Ames Test	TA 98, 100, 1535 and 1537 0, 50, 200, 500, 2000 or 5000 µg/plate with or without liver S9. Acetone used as solvent Repeat assay: 0, 160, 300, 500, 900 or 1600 µg/plate with or without liver S9		**Non mutagenic** Assay was validated with positive control groups.
Salmonella/Ames Test **Methoxyfenozide metabolite: RH-117236 (M-B)**	TA 98, 100, 1535, 1537 or TA 102 0, 50, 200, 500, 2000 or 5000 µg/plate with or without liver S9. DMSO used as solvent Repeat assay: 0, 300, 500, 900, 1600 or 3000 µg/plate with liver S9 or 0, 300, 500, 900 or 1600 µg/plate without liver S9		**Non mutagenic** Assay was validated with positive control groups.
Mammalian gene mutation (in vitro)	CHO cells/(HGPRT locus) 0, 0.5, 1.0, 5.0, 10, 50 or 100 µg/ml with or without liver S9. Acetone used as solvent.		**Non mutagenic** Assay was validated with positive control groups.
Micronucleus Assay (in vivo)	Mouse/CD-1 (5-7/sex/dose) 0, 500, 2500 or 5000 (limit dose) mg/kg bw in 0.5% methyl cellulose.		**Non mutagenic** Assay was validated with positive control groups.
Mammalian cytogenetics (in vitro)	CHO cells 0, 13, 25, 50, 100 or 150 µg/ml with or without liver S9. Acetone used as solvent.		**Non mutagenic** Assay was validated with positive control groups.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/day)	TARGET ORGAN/SIGNIFICANT EFFECTS/COMMENTS
SPECIAL STUDIES			
Acute neurotoxicity	Rat/Crl: CD BR (10/sex/dose) 0, 500, 1000 or 2000 mg/kg bw in 0.5% aqueous CMC; gavage dose.	NOAEL: 2000 mg/kg bw (♂ and ♀) LOAEL: > 2000 mg/kg bw (♂ and ♀)	**No adverse effects observed**
90-d neurotoxicity	Rat/Crl: CD BR (10/sex/dose) 0, 200, 2000 or 20 000 ppm in diet equal to: ♂: 0, 13, 130 or 1318 mg/kg bw/day ♀: 0, 16, 159 or 1577 mg/kg bw/day	NOAEL: ♂: 1318 mg/kg bw/day ♀: 1577 mg/kg bw/day LOAEL: ♂: >1318 mg/kg bw/day ♀: > 1577 mg/kg bw/day	**No adverse effects observed**
Recommended ARfD: Not determined as no toxicological effects could be attributed to a single administration of methoxyfenozide.			
Recommended ADI: 0.10 mg/kg bw/day based on the combined NOAELs of the rat chronic/oncogenicity study (10.2 mg/kg bw/day) and the 1-year dog study (9.8 mg/kg bw/day) and an uncertainty factor of 100 (10× for intra-species variations and 10× for inter-species variations).			

Appendix II Residues

Table 1 Residue summary table

Direction for use						
Crop	**Formulation type**	**Interval (days)**	**Rate (g a.i./ha)**	**Applications/ season**	**Maximum rate (kg a.i./ha)**	**PHI (days)**
Apples	Flowable	10–14	120–240	2	0.48	14

Physicochemical properties	
Water solubility at 20°C (mg/L)	3.3 mg/L
Solvent solubility	Solvent — Solubility (g/kg) n-heptane — 1.87 xylene — 3.38 CH_2Cl_2 — 36.72 methanol — 192.92 2-propanol — 50.22 acetone — 126.88 butyl acetate — 18.76
n-octanol–water partition coefficient (log K_{ow})	3.72 ± 0.04 at 24.7 ± 1.4°C
Dissociation constant (pK_a)	Does not dissociate; not a salt
Vapour pressure (Pa)	< 1.33×10^{-5} Pa at 25, 35 and 45°C (< 1×10^{-7} torr)
Relative density (g/mL)	0.364 ± 0.008 g/mL
Melting point (°C)	204–206°C (TGAI)
UV/visible absorption spectrum	pH — λ (nm) — ε($\times 10^3$) neutral — 203 — 55.3 279 — 2.93 acid — 204 — 51.2 280 — 2.85 alkaline — 219 — 21.3 276 — 3.17

Analytical methodology				
Parameters	**Plant matrices**			
Method ID	TR 34-98-87	TR 34-98-186	TR 34-99-26	TR 34-95-133
Type	Data-gathering and enforcement	Data-gathering	Data-gathering and enforcement	Data-gathering
Analytes	methoxyfenozide	methoxyfenozide	methoxyfenozide	methoxyfenozide

Parameters	Plant matrices			
Instrumentation	HPLC-UV	HPLC-UV; HPLC-MS (celery)	HPLC-UV	HPLC-UV
LOQ	0.025 ppm	0.02 ppm	0.02 ppm	0.025 ppm
Standard	Quantitation of residues from spiked samples was achieved using linear regression analysis of a set of external standards.			
ILV	Successfully validated by an independent laboratory	Not required	Successfully validated by an independent laboratory	Not required
Extraction and clean-up	- Extracted in methanol: 0.1 N HCl and partitioned in hexane and methylene chloride - Clean-up by silica gel and/or Florisil and/or C-18 column	- Extracted in methanol: 0.1 N HCl and partitioned in hexane and methylene chloride - Clean-up by Basic Alumina Column Chromatography and Envir-carbon SPE (all matrices) - For celery: basic alumina column and C-18 column chromatography	- Extracted in methanol: 0.1 N HCl and partitioned in hexane and methylene chloride - Clean-up by Basic Alumina Column Chromatography and Envir-carbon SPE	- Extracted in methanol: 0.1 N HCl and refluxing under reduced pressure -hexane and methylene chloride partitioning - Clean-up by Basic Alumina Column Chromatography and Envir-carbon SPE
Radiovalidation	Adequately radiovalidated	Adequately radiovalidated	Adequately radiovalidated	None

Parameters	Animal matrices
Method ID	TR 34-96-106
Type	Data-gathering and enforcement
Analytes	Methoxyfenozide and metabolite RH-141518
Instrumentation	HPLC-UV: all matrices except liver, kidney; HPLC-MS: liver and kidney
LOQ	0.01 ppm for methoxyfenozide, 0.02 ppm for RH-141518
Standard	An external standard method was used as a marker for retention time, response and calibration using both quantification methods.
ILV	Methoxyfenozide was successfully validated by an independent laboratory in milk, fat, kidney and liver. However, radiovalidation of RH-141518 was incomplete in liver and kidney.

Parameters	Animal matrices
Extraction	Milk, muscle: DCM using matrix solid phase dispersion (MSPD) and ethyl acetate:hexane partitioning Fat: methanol:aqu. HCl and partitioning into DCM. Liver & Kidney: methanol and hexane partitioning
Clean-up	Clean-up (all matrices **except** liver, kidney): alumina column chromatography and carbon SPE. For **liver, kidney**: either C-18 and carbon SPE column chromatography or DCM partitioning and alumina column chromatography
Radiovalidation	Successful radiovalidation was carried out for methoxyfenozide residues in milk and tissues of goat. For RH-141518, there was incomplete radiovalidation in liver and kidney.
Multi-residue method	Multi-residue methods Protocol A through F are **not** suitable for the analysis of methoxyfenozide.

Nature of the residue in apples	
Radiolabel	Methoxyphenyl-^{14}C (MOP)
Test site	Outdoor plot; one single apple tree in Newtown, PA (United States)
Treatment	2 foliar applications made 15 days apart
Rate	1.008 kg a.i./ha + 1.064 kg a.i./ha; total rate 2.072 kg a.i./ha/season
EP	Mixture of unlabelled, [^{13}C] and [^{14}C] methoxyfenozide was formulated in methanol:water (65:35 v:v); final specific activity 7.90 mCi/g
PHI	Apple fruit and apple foliage was harvested immediately after the first application, immediately before and after the second application, and at 7, 14 and 36 days after the second application. Treated foliage was also collected 69 days after the second application (half-life study).

The apple metabolism study demonstrates that residues of methoxyfenozide resulted from uptake and metabolism of methoxyfenozide.

Metabolites identified	**Major metabolites (≥ 10% TRRs)**	**Minor metabolites (< 10% TRRs)**
Radiolabel	**Methoxyphenyl-^{14}C**	**Methoxyphenyl-^{14}C**
14 DAT apples	Methoxyfenozide	RH-131154 RH-131157
36 DAT apples	Methoxyfenozide	RH-131154 RH-131157

Nature of the residue in cotton			
Radiolabel	Methoxyphenyl-^{14}C (MOP)	t-butyl-^{14}C (TB)	Dimethylphenyl-^{14}C (DMP)
Test Site	Outdoor, fenced off plot in Lucama, North Carolina (United States)		
Treatment	Two applications made at 90 and 121 days after planting of a mixture of unlabelled, [^{13}C]- and [^{14}C]-methoxyfenozide		

Rate	2 × 1.075 kg a.i./ha/application; total rate: ~2.15 kg a.i./ha/season (final specific activities: 12.77 mCi/g MOP label; 11.57 mCi/g TB label; 10.65 mCi/g DMP label)
EP	10% emulsifiable concentrate formulations
PHI	**Immature, whole, above-ground cotton plant and boll samples** were collected after the first application, immediately before and after the second application, and at 7 and 14 days after the second application. **Mature bolls and plant samples** were harvested 21 days after the second application.

The cotton metabolism study demonstrates that residues of methoxyfenozide resulted from uptake and metabolism of methoxyfenozide.

Metabolites identified	**Major metabolites (≥ 10% TRRs)**			**Minor metabolites (< 10% TRRs)**		
Radiolabel	**MOP**	**TB**	**DMP**	**MOP**	**TB**	**DMP**
21 DAT cotton (including hulled kernels, hulls/lint and whole cotton seed samples)	Methoxyfenozide			RH-131154	none	none

Nature of the residue in grapes

Radiolabel	T-butyl-^{14}C (TB)
Test site	One single grape vine in an outdoor plot in Newtown, PA (United States)
Treatment	2 foliar applications made 28 days apart to a single grape vine.
Rate	0.986 kg a.i./ha + 1.243 kg a.i./ha; total rate 2.23 kg a.i./ha/season (final specific activity was 9.02 mCi/g)
EP	A mixture of unlabelled, [^{13}C] and [^{14}C] methoxyfenozide was formulated in methanol:water (2:1 v:v)
PHI	Grape fruit and grape foliage was harvested immediately before and after the first application, and at 7, 14 and 21 days after the second application. Treated foliage was also collected 59 days after the second application.

The grape metabolism study demonstrates that residues of methoxyfenozide resulted from uptake and metabolism of methoxyfenozide.

Metabolites identified	**Major metabolites (≥ 10% TRRs)**	**Minor metabolites (< 10% TRRs)**
Radiolabel	**t-butyl-^{14}C**	**t-butyl-^{14}C**
27 DAT grapes	Methoxyfenozide	RH-131364 RH-117236 GLC-RH-117236

Nature of the residue in rice			
Radiolabel	Methoxyphenyl-^{14}C (MOP)	t-butyl-^{14}C (TB)	Dimethylphenyl-^{14}C (DMP)
Test site	Four outdoor plots with separate screen house coverings in California.		
Treatment	Two foliar spray applications made 36 days apart Plot A: mixture of MOP labelled RH-112485; ^{13}C RH-112485 and ^{12}RH-112485. Plot B: mixture of DMP labelled RH-112485; ^{13}C RH-112485 and ^{12}RH-112485. Plot t: mixture of TB-labelled RH-112485; ^{13}C RH-112485 and ^{12}RH-112485. Plot C: untreated control plot. First application: pre-flagleaf stage. Second application: post flowering stage.		
Rate	0.690 kg a.i./ha + 0.370 kg a.i./ha; total rate 1.06 kg a.i./ha/season	2 × 0.6 kg a.i./ha/application; total rate 1.2 kg a.i./ha/season	2 × 0.6 kg a.i./ha/application; total rate 1.2 kg a.i./ha/season
EP	10% emulsifiable concentrate		
PHI	62 days after the last application		

The rice metabolism study demonstrates that residues of methoxyfenozide resulted from the uptake and metabolism of methoxyfenozide.

Metabolites identified	**Major metabolites (≥ 10% TRRs)**	**Minor metabolites (< 10% TRRs)**
Radiolabel	**Methoxyphenyl-^{14}C (MOP)**	
Grain	Methoxyfenozide	RH-131364 RH-117236 RH-131154 RH-131157 RH-141511 GLC-RH-117236
Straw		RH-131364 RH-117236 RH-131154 RH-141511 GLC-RH-117236
Radiolabel	**t-butyl-^{14}C (TB)**	
Grain	Methoxyfenozide	RH-131364 RH-117236 RH-131154 RH-131157 GLC-RH-117236
Straw		RH-131364 RH-117236 RH-131154 RH-141511 GLC-RH-117236

Radiolabel	**Dimethylphenyl-^{14}C (DMP)**	
Grain	Methoxyfenozide	RH-131364 RH-117236 RH-131154 RH-131157 GLC-RH-117236
Straw		RH-131364 RH-117236 RH-131154 RH-141511 GLC-RH-117236

Confined rotational crop study – mustard, radish, wheat			
Radiolabels	Methoxyphenyl-^{14}C (MOP)	t-butyl-^{14}C (TB)	Dimethylphenyl-^{14}C (DMP)
Test Site	Four outdoor plots: one control plot and one treated plot for each label. Each plot was divided into three subplots (one for each planting interval) and each subplot was further divided into three mini plots (one for each crop).		
Treatment	Three applications to bare soil (sandy loam) at a retreatment interval of 3–4 days. Crops were planted in the treated soil at PBI of 31, 91 and 364 days.		
Rate	3 × 0.75 kg a.i./ha/application for a total rate of 2.24 kg a.i./ha/season		
EP	The radioactive test substances were mixed with ^{13}C-methoxyfenozide and unlabelled methoxyfenozide and then formulated as a 5% emulsifiable concentrate formulation (diluted with water).		
PHI	**Immature mustard, radish roots and tops, and wheat forage** were collected at 33–157 days after planting. **Mature mustard and radish** was collected at 47–170 days after planting. **Mature wheat** was collected at 226–257 days after planting.		
Results from this study demonstrate that metabolism of methoxyfenozide is more extensive in rotated field crops than in primary crops, perhaps reflecting soil or plant metabolism.			

Nature of the residue in lactating goats			
Species	**Radiolabel**	**Dose level**	**Sacrifice**
Goat	Methoxyphenyl-^{14}C (MOP) Dimethylphenyl-^{14}C (DMP) t-butyl-^{14}C (TB)	45 ppm 32 ppm 61 ppm	22–23 hrs after final dose
74–84% of administered radioactivity was eliminated in the feces and another 5–7% was eliminated in the urine. A total of 82–88% of the administered radioactivity was recovered in milk, tissues, blood, urine and feces.			

Metabolites identified	Major metabolites (≥ 10% TRRs)	Minor metabolites (< 10% TRRs)
Radiolabel	**Methoxyphenyl-^{14}C (MOP)**	
Milk	Methoxyfenozide	RH-117236 RH-131154 RH-141518 Metabolite H RH-141519
Liver	RH-141518	Methoxyfenozide RH-117236 RH-131154 Metabolite E, F, H RH-141519
Kidney	RH-141518 RH-141519 Metabolite E	Methoxyfenozide RH-117236 RH-131154 Metabolite H
Leg muscle	Methoxyfenozide	RH-117236 RH-131154 Metabolite E
Loin muscle	N/A	N/A
Fat	Methoxyfenozide	RH-117236 RH-141518
Radiolabel	**Dimethylphenyl-^{14}C (DMP)**	
Milk	Methoxyfenozide	RH-117236 RH-131154 Metabolite E, H
Liver	RH-141518	Methoxyfenozide RH-117236 RH-131154 Metabolite E, H RH-141519
Kidney	RH-141518 Metabolite H	Metabolite E RH-141519
Leg muscle	N/A	N/A
Loin muscle	N/A	N/A
Fat	Methoxyfenozide	N/A
Radiolabel	**t-butyl^{14}C (TB)**	
Milk	Methoxyfenozide Lactose	RH-117236 RH-131154 Metabolite E, F, H RH-141518 RH-141519

Liver	RH-141518	Methoxyfenozide RH-117236 RH-131154 Metabolite E RH-141519
Kidney	RH-141518	Methoxyfenozide RH-117236 RH-131154 Metabolite E RH-141519
Leg muscle	Methoxyfenozide Metabolite F	RH-117236 RH-131154 Metabolite E RH-141518
Loin muscle	N/A	N/A
Fat	Methoxyfenozide	N/A

Nature of the residue in laying hens			
Species	**Radiolabel**	**Dose level**	**Sacrifice**
Hen	methoxyphenyl-^{14}C (MOP) dimethylphenyl-^{14}C (DMP) t-butyl-^{14}C (TB)	58 ppm 60 ppm 68 ppm	21–23 hrs after the final dose

84–93% of the administered radioactivity was recovered in the cage wash and excreta. A total of 0.05–0.35% of the administered radioactivity was recovered in the eggs, tissue and blood.

Metabolites identified	**Major metabolites (≥ 10% TRRs)**	**Minor metabolites (< 10% TRRs)**
Radiolabel	**Methoxyphenyl-^{14}C (MOP)**	
Egg	Metabolite E RH-141518 RH-141519	Methoxyfenozide RH-117236 RH-131154 Metabolite F
Liver	RH-141518	Methoxyfenozide RH-117236 RH-131154 Metabolite E, F, H RH-141519
Kidney	RH-141518 RH-141519	Methoxyfenozide RH-117236 Metabolite E
Dark muscle	Methoxyfenozide	RH-117236 RH-131154
Fat	Methoxyfenozide Metabolite E RH-117236	RH-141518 Metabolite F, H

Metabolites identified	Major metabolites (≥ 10% TRRs)	Minor metabolites (< 10% TRRs)
Skin with fat	Methoxyfenozide Metabolite E, F	RH-117236 RH-131154 RH-141518
Radiolabel	**Dimethylphenyl-^{14}C (DMP)**	
Egg	RH-141518 RH-141519 Metabolite E	Methoxyfenozide RH-117236 RH-131154
Liver	RH-141518	RH-141519 RH-117236 Metabolite E
Kidney	RH-141518 RH-141519	RH-117236 Methoxyfenozide Metabolite E, H
Dark muscle	Methoxyfenozide	RH-117236 Metabolite E
Fat	Methoxyfenozide	Metabolite E, F, H RH-117236 RH-141518
Skin with fat	Methoxyfenozide Metabolite E	Metabolite F RH-117236 RH-141518 RH-131154
Radiolabel	**t-butyl-^{14}C (TB)**	
Egg	RH-141518 RH-141519	Methoxyfenozide RH-117236 RH-131154 Metabolite E, F, H
Liver	N/A	RH-141518 RH-141519 Methoxyfenozide RH-117236 RH-131154 Metabolite E
Kidney	N/A	RH-141518 RH-141519 Metabolite E, H RH-117236
Dark muscle	RH-141518 RH-141519	Methoxyfenozide RH-117236 Metabolite E, F

Metabolites identified	Major metabolites (≥ 10% TRRs)	Minor metabolites (< 10% TRRs)
Light muscle	RH-141518	Metabolite E, F, H Methoxyfenozide RH-117236 RH-131154 RH-141519
Fat	Methoxyfenozide	RH-117236 RH-141519 Metabolite E
Skin with fat	Methoxyfenozide RH-141518	RH-117236 RH-131154 Metabolite E, F RH-141519

Crop field trials – apples

Twelve apple trials were conducted in Canada and the United states in 1999 (one in each of Zone 1, 1A; three each in Zones 5B, 11 and four in Zone 5).

Commodity	Rate (kg a.i./ha)	PHI (days)	Methoxyfenozide residue levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	SD
RH-2485									
Apples	1.44 (3.0×)	14–15	24	0.09	0.587	0.523	0.254	0.284	0.13

Residue decline – apples

One trial (St. George, ON, Zone 5) conducted a residue decline study, where apples were collected at 1, 3, 7, 14 and 18 days after the last application (DALA). Results show unexpectedly low residue levels from the samples collected at 1, 3 and 7 DALA (0.0227–0.0429 ppm). Samples collected at 18 DALA had only slightly lower residue levels than the 14 DALA samples (0.208 ppm versus 0.262 ppm), indicating that there is no significant decline in residues with increasing PHIs.

Commodity	Rate (kg a.i./ha)	PHI (days)	Methoxyfenozide residue levels (ppm)						
			n	Min.	Max.	HAFT	Median	Mean	SD
RH-2485									
Apples	1.46	1	2	0.03	0.04	N/A	0.037	0.04	0.008
		3	2	0.02	0.03		0.026	0.03	0.004
		7	2	0.02	0.03		0.026	0.03	0.004
		14	4	0.243	0.279		0.261	0.262	0.016
		18	2	0.201	0.215		0.208	0.208	0.1

Processing studies

Two apple processing studies were carried out. In one study, fruit was treated with Intrepid 80W (80% methoxyfenozide) at a rate of 2.02 kg a.i./ha then either washed or peeled. In the other study, apples were treated with Intrepid 2F (23% methoxyfenozide) at a rate of 2.02 kg a.i./ha and either processed into apple juice or into wet apple pomace. The rates used in both studies represent exaggerated rates to the current proposed Canadian label rate for apples. Results indicate that expected residues in/on washed apples, peeled apples and apple juice will be covered my the MRL set on the RAC. For wet apple pomace (6.0× concentration factor), an evaluation of the transfer of methoxyfenozide residues to livestock tissue and milk was assessed in the livestock feeding study.

Fraction	Mean residue levels (ppm)	Calculated concentration factor
Washed apples	0.181–0.689	1.1×
Peeled apples	0.059–0.137	0.3×
Apple juice	0.06	0.2×
Wet apple pomace	1.59	6×

Livestock feeding

A cattle feeding study was required since methoxyfenozide residues were found to concentrate in wet apple pomace (6.0×) which is a feed item for cattle. In the study, lactating cattle were administered methoxyfenozide at a rate of 0, 19.5, 59.6, and 192 ppm in gelatin capsules for 28 days (0, 415, 1246, and 4154 mg methoxyfenozide/21–22 kg feed, respectively). In the framework of the current submission for a domestic registration on apples only, wet apple pomace is the only feed item. Therefore, the following MTDB values were calculated: 1.59 ppm for cattle, 0 ppm for hog, and 0 ppm for poultry. Based on these values, it is not likely that residues on methoxyfenozide will be quantifiable in any animal matrices. Therefore, from a regulatory perspective, no action is required in the framework of the current submission.

However, in order to be protective of the Canadian population for **risk assessment purposes**, MTDBs were also calculated to investigate the anticipated level of methoxyfenozide residues in animal commodities based on the extended use pattern in the United States. The recalculated MTDB values are 82.3 ppm for cattle, 1.23 ppm for hogs, and 0.84 ppm for poultry.

Based on these numbers, results from the closest feeding level from the cattle feeding study (192 ppm) showed quantifiable residues of methoxyfenozide in raw milk (0.057 ppm), skim milk (0.007 ppm), cream (0.213 ppm), fat (0.44 ppm), and muscle (0.01 ppm). Similarly, combined residues of methoxyfenozide plus RH-141518 (adjusted for maximum degradation of 40% as per freezer storage stability results) were quantifiable in liver and in kidney (0.412 ppm and 0.136 ppm, respectively). Therefore in order to account for the highest possible levels of methoxyfenozide residues in animal commodities for risk assessment purposes, these values will be used as anticipated residue values for cattle matrices during the dietary risk assessment.

For hog and poultry matrices, results from the closest feeding level in the cattle and poultry feeding study, respectively, showed that residues would not likely be quantifiable in any hog or poultry matrices. Therefore, anticipated residue values were not used for hog or poultry matrices during the dietary risk assessment.

Storage stability

Apples: Residues of methoxyfenozide were shown to be stable in apples, apple juice, and wet apple pomace for 12 months, 9.4 months and 10 months, respectively. Freezer storage stability data for washed and peeled apples was not available. These results adequately support the storage conditions of the apple field samples and apple processed commodities, stored frozen for 12 months and 7 months, respectively.

Livestock commodities: Residues of methoxyfenozide were shown to be stable for 3.5 months in milk, 5.4 months in cow muscle, 8.6 months in cow liver and 8.7 months in cow kidney. Metabolite RH-141518 was stable for the first five months in cow kidney but declined 13–29% after six to nine months of frozen storage. Similarly, in cow liver, residues of RH-141518 declined by 20–40% after less than one month of freezer storage, but showed no further decline for up to nine months. Therefore, an adjustment factor is needed for liver and kidney samples in the animal feeding studies.		
Plant studies – apples, grapes, cotton, rice		
ROC for enforcement and risk assessment: **Plants** **Rotational crops**	Methoxyfenozide Not applicable since registration is for orchard crops only.	
Metabolic profile in diverse crops	Hydrolysis followed by conjugation in a limited number of positions	
Animal studies – goat and hen		
Animal	**Goat**	**Hen**
ROC for enforcement and risk assessment	**Milk and tissues of ruminants (except liver and kidney):** Methoxyfenozide **Liver and kidney:** Methoxyfenozide plus Metabolite RH-141518	**Eggs and tissues of poultry:** Methoxyfenozide plus Metabolite RH-141518
Metabolic profile in animals	Qualitatively and quantitatively similar	
Fat-soluble residue	No	

Table 2 Dietary risk from food and water

Chronic non-cancer dietary risk ADI = 0.1 mg/kg bw EEC = 0.101 ppm Chronic dietary exposure analyses were performed in order to determine the exposure and risk estimates which resulted from the use of methoxyfenozide on apples in Canada, including imported into Canada (from the United States). The assessment used the maximum residues limits and assumed 100% crop treated.	POPULATION	ESTIMATED RISK (% of ADI)			
		Food (Basic)	Food (Refined)	Food + EEC (Basic)	Food + EEC (Refined)
	All infants < 1 yr old	20.2	10.2	27.2	17.2
	Children 1 to 2 yrs	36.2	18.6	39.4	21.8
	Children 3 to 5 yrs	31.8	18.3	34.8	21.2
	Children 6 to 12 yrs	22.2	14.4	24.2	16.4
	Youth 13 to 19 yrs	16.3	11.8	17.8	13.4
	Adults 20 to 49 yrs	18	14.3	20	16.3
	Adults 50+ yrs	18.4	14.9	20.5	17
	Females 13 to 49 yrs	18.2	14.4	20.1	16.4
	Total Population	19.6	14.5	21.8	16.6
ARfD	N/A				
Q*	N/A				

Appendix III Environmental assessment

Table 1 Physical and chemical properties of the active ingredient relevant to the environment

Property	Value	Comments
Water solubility	3.3 mg/L	The solubility of the active ingredient in water is classified as low.
Vapour pressure at 25°C	$< 1.33 \times 10^{-5}$ Pa ($< 1 \times 10^{-7}$ torr)	According to Kennedy and Talbert (1977), the active ingredient is non-volatile.
Henry's Law constant	1.935×10^{-7} atm·m^3/mol 1.263×10^{5} (1/H)	Non-volatile from water and moist soil surfaces.
log K_{ow}	3.72 ± 0.04 at 24.7 ± 1.4°C	There is potential for the active ingredient to bioconcentrate.
pK_a	none	The active ingredient is not expected to dissociate in water.
UV–visible absorption	pH / λmax (nm) / ε neutral 203 55 313 279 2932 acid 204 51 183 280 2855 alkaline 219 21 317 276 3170	A UV absorption maximum for the active ingredient was found at 203 nm; therefore, the active ingredient has a low potential for UV light-induced phototransformation under normal environmental conditions. A visible light spectrum was not submitted; therefore, no prediction can be made on the potential for visible light-induced phototransformation.

Table 2 Fate and behaviour in the terrestrial environment

Property	Test substance	Value	Comments
Abiotic transformation			
Hydrolysis	Methoxyfenozide	pH 5: 587 d pH 7: 1572 d pH 9: 695 d	Not a route of transformation in the environment.
Phototransformation on soil	Methoxyfenozide	173 d	Not a route of transformation in the environment.
Biotransformation			
Biotransformation in aerobic soil	Methoxyfenozide	573 d (loam) 722 d (sandy clay loam) 336–1100 d (loamy sand)	A route of transformation in the environment. Methoxyfenozide is persistent in soil under aerobic conditions.
Mobility			
Adsorption in soil	Methoxyfenozide	Adsorption K_{oc} (L/kg) loam: 267 loamy sand: 200.2–922 sandy loam: 219–330.6 silt loam: 314.1–365 silty clay: 318.4	In the soils tested, methoxyfenozide is classified as follows: • moderately mobile in loam, sandy loam, and silty loam soils; and • has low to moderate mobility in loamy sand soil.

Property	Test substance	Value	Comments
Field studies			
Field dissipation	Intrepid 240F	**Canadian study:** DT_{50} for Ecoregion 5.3 (Atlantic Highlands of the Northern Forests): 433 d DT_{50} for Ecoregion 8.1 (Mixed Wood Plains of the Eastern Temperate Forest): 239 d DT_{50} for Ecoregion 6.2 (Western Cordillera of the Northwestern Forested Mountains): 330 d **American study:** DT_{50} for Ecoregion 10.1 (North American Deserts): 268 d	Turf-covered soil plots were studied. Persistent under field conditions. There is potential for carryover. Bare plots were studied. Persistent under field conditions.

Table 3 Fate and behaviour in the aquatic environment

Property	Test substance	Value	Comments
Abiotic transformation			
Hydrolysis	Methoxyfenozide	Half-lives: pH 5: 587 d pH 7: 1572 d pH 9: 695 d	Not an important route of transformation in the environment.
Phototransformation in water	Methoxyfenozide	Stable	Not a route of transformation.
Biotransformation			
Biotransformation in aerobic water/sediment systems	Methoxyfenozide	DT_{50}: 387–963 d (whole system)	A route of transformation. Methoxyfenozide partitions to sediment where it is persistent.

Property	Test substance	Value	Comments
Biotransformation in anaerobic water/sediment systems	Methoxyfenozide	DT_{50}: 654 d (whole system)	Not an important route of transformation in the environment.
Bioconcentration	Methoxyfenozide	Depuration half-life: < ½ days	Depurated quickly from fish

Table 4 Maximum EEC in vegetation and insects after a direct overspray of methoxyfenozide at the maximum annual application rate 480 g a.i./ha for apples (2 applications of 240 g a.i./ha)

Matrix	EEC (mg a.i./kg fw)[a]	Fresh to dry weight ratios	EEC (mg a.i./kg dw)
Short-range grass	103	3.3[b]	340
Leaves and leafy crops	53.8	11[b]	590
Long grass	47.0	4.4[b]	205
Forage crops	57.6	5.4[b]	310
Small insects	25.0	3.8[c]	95
Pods with seeds	5.1	3.9[c]	20.0
Large insects	4.3	3.8[c]	16.2
Grain and seeds	4.3	3.8[c]	16.2
Fruit	6.4	7.6[c]	48.9

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)
[b] Fresh to dry weight ratios from Harris (1975)
[c] Fresh to dry weight ratios from Spector (1956)

Table 5 Maximum EEC of methoxyfenozide in diets of birds and mammals at the maximum annual application rate of 480 g a.i./ha for apples (2 applications of 240 g a.i./ha)

Organism	Matrix	EEC (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	84
Mallard duck	30% large insects 70% grain	16.2
Rat	70% short grass 20% grain/seeds 10% large insects	242

Organism	Matrix	EEC (mg a.i./kg dw diet)
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	241

Table 6 Effects on terrestrial organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity
Invertebrates				
Earthworm *(Eisenia fetida)*	Acute	Methoxyfenozide	LC_{50}: > 1213 mg a.i./kg dw substrate NOEC: 1213 mg a.i./kg dw substrate	Non-toxic up to 1213 mg a.i./kg dw
Bee *(Apis mellifera L.)*	Oral	Methoxyfenozide	LC_{50}: > 100 µg a.i./bee	Practically non-toxic[a]
	Contact	Methoxyfenozide	LC_{50}: > 100 µg a.i./bee	Practically non-toxic[a]
Birds				
Bobwhite quail *(Colinus virginianus)*	Acute	Methoxyfenozide	LD_{50}: > 2250 mg a.i./kg bw NOEC: 2250 mg a.i./kg bw	Practically non-toxic[b]
	Acute dietary (5-d)	Methoxyfenozide	LC_{50}: > 5620 mg a.i./kg diet NOEC: 5620 mg a.i./kg diet	Practically non-toxic[b]
Mallard duck *(Anas platyrhynchos)*	Acute dietary (5-d)	Methoxyfenozide	LC_{50}: > 5620 mg a.i./kg diet NOEC: 562 mg a.i./kg diet	Practically non-toxic[b]
	Reproduction	Methoxyfenozide	LOEC:1000 mg a.i./kg dw diet NOEC: 780 mg a.i./kg diet	—
Mammals				
Refer to Section 3.0 and Appendix I.				

[a] Atkins et al. (1981) for bees
[b] USEPA classification

Table 7 Effects on aquatic organisms

Organism	Exposure	Test substance	Endpoint value	Degree of toxicity[a]
Freshwater species				
Daphnia magna	Acute	Methoxyfenozide (99.2%)	EC_{50}: > 3.3 mg a.i./L NOEC: 1.7 mg a.i./L	Moderately toxic
	Chronic	Methoxyfenozide (99.2%)	NOEC: 0.20 mg a.i./L LOEC: 0.39 mg a.i./L	—
Chironomid (*Chironomus riparius*)	Chronic	Methoxyfenozide (99.2%)	EC_{50} for water: 0.014 mg a.i./L NOEC for water: 0.0065 mg a.i./L	—
	Chronic	RH-117236 (transformation product)	NOEC: < 0.1 mg/L LOEC: 0.1 mg/L	—
Rainbow trout (*Onchorhynchus mykiss*)	Acute	Methoxyfenozide (98%)	LC_{50}: > 3.3 mg a.i./L NOEC: 3.3 mg a.i./L	Moderately toxic
Bluegill sunfish (*Lepomis macrochirus*)	Acute	Methoxyfenozide (98%)	LC_{50}: > 3.3 mg a.i./L NOEC: 3.3 mg a.i./L	Moderately toxic
Fathead minnow (*Pimephales promelas*)	Chronic	Methoxyfenozide	Whole life-cycle study (262 d) LC_{50}: > 3.3 mg a.i./L NOEC: 0.53 mg a.i./L LOEC: 1.0 mg a.i./L	—
Marine species				
Crustacean–mysid shrimp (*Mysidopsis bahia*)	Acute	Methoxyfenozide	96-h LC_{50}: 1.3 mg a.i./L NOEC: 0.68 mg a.i./L	Moderately toxic
	Chronic	Methoxyfenozide	37-d NOEC: 51 µg a.i./L LOEC: 100 µg a.i./L	—
Mollusc—Eastern oyster (*Crassostrea virginica*) shell deposition	Acute	Methoxyfenozide	(Eastern oyster) EC_{50}: 1.2 mg a.i./L NOEC: 0.4 mg a.i./L	Moderately toxic
Sheepshead minnow (*Cyprinodon variegatus*)	Acute	Methoxyfenozide	LC_{50}: > 2.8 mg a.i./L NOEC: 2.8 mg a.i./L	Moderately toxic

[a] USEPA classification, where applicable

NOTE: 3.3 mg a.i./L is the limit of solubility

Table 8 Risk to terrestrial organisms

Organism	Exposure	Test material	Endpoint value	EEC	Risk quotient	Risk
Invertebrates						
Earthworm	Acute	Methoxyfenozide	1213 mg a.i./kg dw	0.21 mg a.i./kg soil	0	Negligible
Bee	Oral	Methoxyfenozide	> 112 kg a.i./ha	0.21 mg a.i./kg soil	0.013	—
	Contact	Methoxyfenozide	> 112 kg a.i./ha	0.21 mg a.i./kg soil	0.013	—
Birds						
Bobwhite quail	Acute	Methoxyfenozide	2250 mg a.i./kg bw	84.0 mg a.i./kg bw	189 days**	Negligible
	5-d dietary	Methoxyfenozide	5620 mg a.i./kg bw	84.0 mg a.i./kg bw	0.01	Negligible
Mallard duck	5-d dietary	Methoxyfenozide	562 mg a.i./kg diet	16.2 mg a.i./kg dw	0.03	Negligible
	Repro-duction	Methoxyfenozide	780 mg a.i./kg diet	16.2 mg a.i./kg dw	0.02	Negligible
Mammals						
Rat	Acute	Methoxyfenozide	500 mg a.i./kg bw	242 mg a.i./kg dw	12 days††	Negligible
	2-yr dietary	Methoxyfenozide	200 mg a.i./kg dw	242 mg a.i./kg dw	1.2	Moderate
	Repro-duction	Methoxyfenozide	2000 mg a.i./kg dw	242 mg a.i./kg dw	0.12	Low
Mouse	Acute	Methoxyfenozide	500 mg a.i./kg bw	241 mg a.i./kg dw	12 days‡‡	Negligible
	3-month dietary	Methoxyfenozide	7000 mg a.i./kg dw	241 mg a.i./kg dw	0.03	Negligible

For apples (2 × 240 g a.i./ha)

** For bobwhite quail acute oral toxicity, FC was 0.027 kg dw/ind/day; BWI was 0.193 bw/ind; DI (= FC × EEC) was 2.3 mg a.i./ind/d; and the $NOEL_{ind.}$ (= NOEL × BWI) was 434 mg a.i./ind. The number of days for a wild population to reach the NOEL in the laboratory population was calculated as $NOEL_{ind.}$/DI (=189 d).

†† For rat acute oral toxicity, FC was 0.06 kg dw/ind/day; BWI was 0.35 bw/ind; DI (= FC × EEC) was 14.5 mg a.i./ind/d; and the $NOEL_{ind.}$ (= NOEL × BWI) was 175 mg a.i./ind. The number of days for a wild population to reach the NOEL in the laboratory population was calculated as $NOEL_{ind.}$/DI (= 12 d).

‡‡ For mouse acute oral toxicity, FC was 0.006 kg dw/ind/day; BWI was 0.033 bw/ind; DI (= FC × EEC) was 1.4 mg a.i./ind/d; and the $NOEL_{ind.}$ (= NOEL × BWI) was 16.5 mg a.i./ind. The number of days for a wild population to reach the NOEL in the laboratory population was calculated as $NOEL_{ind.}$/DI (= 12 d).

Table 9 Risk to aquatic organisms

Organism	Exposure	Application rate/year (g a.i./ha)	Endpoint value	EEC	Risk quotient	Risk
Freshwater species						
Daphnia magna	Acute	Methoxyfenozide	1.7 mg a.i./L	0.16 mg a.i./L	0.09	Negligible
	Chronic	Methoxyfenozide	0.20 mg a.i./L	0.16 mg a.i./L	0.8	Low
Chironomid	Chronic	Methoxyfenozide	0.0026–0.0065 mg a.i./L	0.16 mg a.i./L	25–62	High
	Chronic	RH-117236	< 0.1 mg a.i./L	0.016 mg a.i./L	0.16	Low
Rainbow trout	Acute	Methoxyfenozide	3.3 mg a.i./L	0.16 mg a.i./L	0.04	Negligible
Bluegill sunfish	Acute	Methoxyfenozide	3.3 mg a.i./L	0.16 mg a.i./L	0.04	Negligible
Fathead minnow	Chronic (whole life-cycle toxicity)	Methoxyfenozide	0.53 mg a.i./L	0.16 mg a.i./L	0.3	Low
Marine species						
Crustacean (*Mysidopsis bahia*)	Acute	Methoxyfenozide	0.68 mg a.i./L	0.16 mg a.i./L	0.23	Low
	Chronic	Methoxyfenozide	0.051 mg a.i./L	0.16 mg a.i./L	3.1	Moderate
Mollusc (*Crassostrea virginica*)	Acute	Methoxyfenozide	0.40 mg a.i./L	0.16 mg a.i./L	0.4	Low
Sheepshead minnow	Acute	Methoxyfenozide	2.8 mg a.i./L	0.16 mg a.i./L	0.06	Negligible

References

Atkins, E.L., E.A. Greywood and R.L. Macdonald. 1975. *Toxicity of Pesticides and Other Agricultural Chemicals to Honey Bees: Laboratory Studies*. University of California, Division of Agricultural Sciences.

Atkins, E. L., D. Kellum and K.W. Atkins. 1981. *Reducing Pesticide Hazards to Honey Bees: Mortality Prediction Techniques and Integrated Management Strategies*. University of California, Division of Agricultural Sciences, Leaflet 2883. p. 22.

Goring, C.A.I., D.A Laskowski, J.H. Hamaker and R.W. Meikle. 1975. "Principles of Pesticide Degradation in Soil" in R. Haque and V.H. Freed (eds.). *Environmental Dynamics of Pesticides*. Plenum Press, New York. pp. 135–172.

Hassan S.A. et al. 1994. Results of the sixth joint pesticide testing programme of the IOBC/WPRS–working group "Pesticides and beneficial organisms". *Entomophaga*. 39(1):107–119.

Hoerger, F., and E.E. Kenaga. 1972. "Pesticide Residues on Plants: Correlation of Representative Data as Basis for Estimation of Their Magnitude in the Environment" in Coulston F; Korte F. (eds). *Global Aspects of Chemistry, Toxicology and Technology as Applied to the Environment*, Vol. I. Thieme, Stuttgart, and Academic Press, New York. pp. 9–28.

Kenaga, E.E. 1973. "Factors to be Considered in the Evaluation of the Toxicity of Pesticides to Birds in their Environment" in Coulston F; Dote F. (eds). *Global Aspects of Chemistry, Toxicology and Technology as Applied to the Environment*, Vol. II. Thieme, Stuttgart, and Academic Press, New York. pp. 166–181.

Kennedy, J.M., and R.E Talbert. 1977. "Comparative Persistence of Dinitroaniline Type Herbicides on the Soil Surface". *Weed Science*. 25:373-381.

Knight, A. 2004. *A 40-year Experiment: Codling Moth's Responses to Guthion and Other Insecticides*. Proceedings of the 78th Western Orchard Pest and Disease Management Conference, Portland, Oregon, 14–16 January 2004.

MacLeod, D.A. 1994. *Statistical Analysis Methods for Avian Reproduction Experiments*. Technical Report Series No. 211. Canadian Wildlife Services, National Wildlife Research Centre, Environment Canada. Hull, Quebec.

McCall, J.P., D.A. Laskowski, R.L. Swann and J.J. Dishburger. 1981. "Measurement of Sorption Coefficients of Organic Chemicals and Their Use in Environmental Fate Analysis" in *Test Protocols for Environmental Fate and Movement of Toxicants*. Proceedings of a symposium. Association of Official Analytical Chemists. 94th Annual Meeting, 21–22 October 1980 Washington, DC. pp. 89–109.

Merritt, R.W., and K.W. Cummins (eds). *An Introduction to the Aquatic Insects of North America*. 3rd ed. Kendall/Hunt Publishing, Iowa.

Mineau, P., B. Jobin and A. Baril. 1994. *A Critique of the Avian 5-day Dietary Toxicity Test (LC_{50}) as the Basis of the Avian Risk Assessment*. Environment Canada, Technical Report Series No. 215. 23 pp.

Reice, S.R., and M. Wohlenberg. 1993. "Monitoring Freshwater Benthic Macroinvertebrates and Benthic Processes: Measures for Assessment of Ecosystem Health", in D.M. Rosenberg and V.H. Resh (eds.). *Freshwater Biomonitoring and Benthic Macroinvertebrates*. Chapman and Hall, New York. pp. 287–305.

Smirle, M.J., D.T. Lowry and C. Zurowski. 2002. "Resistance and Cross-resistance to Four Insecticides in Populations of Obliquebanded Leafroller (Lepidoptera: Tortricidae)". *Journal of Economic Entomology*. 95: 820–825.

Urban, D.G. and N.J. Cook. 1986. *Ecological Risk Assessment*. United States Environmental Protection Agency, EPA 540.9-85-001. Washington, D.C. 96 pp.

USEPA. 1985a. *Hazard Evaluation Division, Standard Evaluation Procedure, Avian Single-Dose Oral LD50 Test*. EPA 540/9-85-007. June, 1985. USEPA, Washington, D.C.

USEPA. 1985b. *Hazard Evaluation Division, Standard Evaluation Procedure, Avian Dietary LC50 Test*. EPA 540/9-85-008. June 1985. USEPA, Washington, D.C.

USEPA. 1985c. *Hazard Evaluation Division, Standard Evaluation Procedure, Acute Toxicity Test for Freshwater Invertebrates*. EPA 540/9-85-005. June 1985. USEPA, Washington, D.C.

USEPA. 1985d. *Hazard Evaluation Division, Standard Evaluation Procedure, Acute Toxicity Test for Freshwater Fish*. EPA 540/9-85-006. June 1985. USEPA, Washington, D.C.

USEPA. 1985e. *Hazard Evaluation Division, Standard Evaluation Procedure, Acute Toxicity Test for Estuarine and Marine Organisms (Shrimp 96-Hour Acute Toxicity Test)*. EPA 540/9-85-010. June 1985. USEPA, Washington, D.C.